HEALTH EFFECTS OF CADMIUM

AND

ITS INORGANIC COMPOUNDS

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TABLE OF CONTENTS

	PAGE
1. INTRODUCTION	1
2. PHYSICAL AND CHEMICAL PROPERTIES	2
2.1 Geology	2
2.2 Chemistry	2
2.3 Industrial Use	3
2.4 Sources of Exposure	4
2.4.1 Environmental	4
2.4.2 Occupational	5
2.4.3 Tobacco Smoking	7
2.5 Measurement and Biological Monitoring	7
3. TOXICOKINETICS	9
3.1 Absorption	10
3.1.1 Respiratory Absorption	10
3.1.2 Gastrointestinal Absorption	11
3.2 Tissue Deposition	12
3.2.1 Metallothionein	16
3.3 Excretion	19
3.4 Biological Half-time	20
3.5 Significance of Blood and Urine Cadmium Concentrations	21
3.5.1. Urine Cadmium Concentrations	21
3.5.2. Blood Cadmium Concentrations	22
4. TOXICOLOGY 22	
4.1 Acute Effects	23
4.1.1 Respiratory Effects	23
4.1.2 Gastrointestinal Effects	25
4.1.3 Other Acute Toxic Effects	26

4.2 Chronic Effects 26

4.2.1 Renal Effects 27

4.2.2 Respiratory Effects 35

4.2.3 Effects on Bone 39

4.2.4 Cardiovascular Effects and Hypertension 40

4.2.5. Mutagenic and Carcinogenic Effects 41

4.2.5.1. Mutagenesis 42

4.2.5.2. Carcinogenesis 44

4.2.5.2(a)Animal Carcinog. Studies 44

4.2.5.2(b)Human Carcinog. Studies 47

4.2.6 Reproductive Effects 54

4.2.7 Other Effects 54

5. EXPOSURE-EFFECT RELATIONSHPS (EPIDEMIOLOGY) 55

6. RELATIONSHIP BETWEEN EXPOSURE TO CADMIUM AND CADMIUM CONTENT OF KIDNEY CORTEX 58

6.1 Description of Model 58

6.2 Limitations of Models 67

6.3 Results of Model Calculations 68

6.4 Discussion 69

7. SUMMARY AND CONCLUSIONS 70

8. RECOMMENDATION 73

9. ADDENDUM (Cadmium Pigments) 74

10. REFERENCES 1-15a

11. FIGURES & TABLES

1. INTRODUCTION

The total metal content of the earth's crust is constant and metals are redistributed as a result of human activities such as industrial production, waste disposal, the use of sewage sludge and super-phosphate fertilizers, fossil fuel combustion and natural processes (volcanic eruptions, forest fires, etc.). Cadmium is of special importance to occupational health because it is widely used in industry and this element has a long biological half-life* (approximately 10-30 years) in humans (Friberg, 1974; Webb, 1979; Friberg, 1979; Lauwerys, 1982).

Because cadmium accumulates in tissues and has a wide range of toxic effects in humans, it is important to limit and control the exposure of workers to cadmium. Concern has recently been growing about the industrial use of cadmium and its effect on human health. Sweden (Swedish Env. Prot. Board, 1981) has enforced restrictions on the use of cadmium for pigments, stabilizers and coatings. Denmark and West Germany also plan to restrict the industrial use of certain cadmium compounds (Markard, 1983). A World Health Organization Study Group has recently recommended strict exposure limits for cadmium based on the long-term health effects (WHO, 1980).

This document will attempt to provide a critical assessment of the potential risks to human health

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* biological half-life is used in this introductory paragraph however the term half-time will be used in the remainder of the document as it seems more appropriate in the study of cadmium.

associated with occupational exposure to cadmium and to evaluate the available dose-response data. Laboratory tests which are considered to be indices of both exposure to and body burden of, cadmium will be assessed.

2. PHYSICAL AND CHEMICAL PROPERTIES

2.1 Geology

Cadmium is a relatively rare metal with an estimated average abundance in the earth's crust of 0.55 grams per metric ton. It is an ubiquitous element found as an impurity, mainly in zinc ore deposits, but also in other non-ferrous metal ores. Although there are no known deposits of cadmium ores, cadmium is an unavoidable part of the non-ferrous metals industry all over the world.

The primary geological occurrence is greenockite (CdS) which is usually found combined with sphalerite (ZnS) and sometimes in more complex mixtures (Fulbertson, 1973).

The ratio between anthropogenic flux and natural flux describes the importance of the man-made contribution to the total flux of a metal. Cadmium is among the metals with a relatively low natural flux and a large anthropogenic flux (Lantzy, 1979).

2.2 Chemistry

Cadmium is classified as a non-transition element (number 48) in Group IIB of the periodic table and has an atomic weight of 112.4. Two and zero are its only stable valencies.

The organometallic compounds of cadmium such as methyl cadmium are characterized by a covalent bond between

cadmium and carbon. They are unstable and are rapidly decomposed (Friberg, 1979). Therefore, the major forms of cadmium found in nature are the many inorganic compounds, of which cadmium oxide and sulfide are almost insoluble, while several salts of cadmium such as acetate, chloride and sulfate are quite soluble in water.

Because of its relatively low boiling point (765°C) and relatively high vapour pressure (16mm Hg at 500°C), cadmium may be vapourized more easily than zinc and may release fumes during operations at high temperatures. These fumes oxidize and become transformed into aerosols of cadmium oxide, most of which consists of fine particulate matter, in the respirable range. The toxicity of the different compounds of cadmium occurring in industry depends upon the cadmium ion, although the hazard may vary depending upon the solubility of the compound.

2.3 Industrial Use

Cadmium is highly corrosion resistant and is used as a protective coating for iron, steel and copper. It is generally applied by electro-plating, but hot dipping and spraying are possible. Cadmium may be alloyed with copper, nickel, gold, silver, bismuth and aluminium to form low melting-temperature compounds. These alloys may be used as coatings for other materials, welding electrodes, silver-cadmium electrical contacts and solders. These uses account for a large percentage of cadmium consumption. It is also utilized in alkaline storage batteries, stabilizers for polyvinylchloride plastics, a deoxidizer in nickel plating, in amalgams in dentistry, in the manufacture of fluorescent lamps, semi-conductors, photo-cells, in jewellery, in process engraving, and in the automobile and aircraft industries.

Cadmium compounds are used in fungicides, insecticides, nematocides, polymerization catalysts and pigments in paint and glass. They are also used in the photographic industry and in glazes.

Production of cadmium in Ontario amounted to 791,333 kg, 609,215 kg and 475,000 kg for the years 1980 to 1982, respectively (the 1982 figure is a preliminary estimate). These figures appear to be for Ontario's sole producer of pure cadmium, Kidd Creek Mines. Most of the cadmium produced is exported, particularly to the U.S. There are three other Ontario producers of cadmium, their product is in the form of zinc concentrates which are shipped out of the province for further refining - Geco Division of Noranda, Mattaby and Celco Inc. At the time this document was being prepared (1984) Celco was closed down.

2.4 Sources of Exposure

Environmental

The major environmental source of cadmium for non-smokers is food with a small contribution from water. The cadmium content of air in unpolluted areas is negligible and it contributes little to the daily intake. Tobacco contains appreciable amounts of cadmium and may therefore, in smokers, be the major source of exposure. Industrial workers are exposed to cadmium mainly by inhalation but also by ingestion. Dermal absorption of cadmium is of no significance.

Although studies indicate that foodstuffs generally contain less than 0.05 ppm cadmium (wet weight), certain foods, such as leafy vegetables, mushrooms, grains, shellfish, beef liver and kidney may contain much higher quantities of cadmium, even in unpolluted areas (Friberg,1974; Sandi,1979). Since certain plants absorb

cadmium from water, soil and fertilizers (especially super-phosphate and sewage sludge fertilizers), they may contribute significantly to the daily intake of cadmium.

The daily intake of cadmium has been estimated in diets in several countries. An extensive study in the U.K. estimated the intake of cadmium to be between 10 and 30 µg for a 70 kg person (U.K. Min. of Agr., 1973). Swedish estimates (Kjellstrom, 1979) suggest a daily intake of about 10-20 µg/day while an average daily intake in the U.S.A. (Mahaffey, 1975) may be about 39 µg. The cadmium content of the Canadian diet (Webb, 1975) may be slightly higher (60-80 µg/day). Since 90-95% of ingested cadmium remains unabsorbed, the measurement of faecal cadmium may provide an approximate estimate of daily oral intake of cadmium (Kjellstrom, 1979). Differences in oral intake in the general population have been estimated by this method. However, this type of estimation has little value in monitoring occupational exposure to cadmium because most occupational exposure is by inhalation.

Occupational

Metallic cadmium is produced commercially as a by-product of primary metal industries, principally the zinc industry. Cadmium is also found in lead, copper and other ores that contain zinc minerals. Cadmium is released from these, either through volatilization or through washing and solubilization. The comparatively low boiling point of cadmium favors volatilization of the metal in heating processes such as ore roasting, pyrosmelting and steel scrap melting. Accidental releases of cadmium fumes from chemical and electroplating plants also have been reported (Beton, 1966). A number of these occupational exposures can be

prevented by suitable engineering controls. Most sources of occupational exposure to cadmium are also potential sources of environmental exposure.

The literature contains references to a very wide range of ambient levels of cadmium in industrial plants. High levels of air cadmium concentrations were reported to have occurred in industries about thirty years ago but most of the current exposure levels are very much lower than these values. In 1950, Friberg reported that the cadmium concentration in the air of a Swedish cadmium-nickel battery factory to be as high as 1000 to 10,000 micrograms of cadmium per cubic metre of air (µg Cd/m^3). Follow-up studies suggest that by 1979 the exposure level had been reduced to 5-10 µg Cd/m^3 in the same factory (Friberg, 1979). Reports from British factories also show wide variations in exposure levels. During 1960-1969, average exposure levels of 500 µg Cd/m^3 in a battery factory and 20-106 µg Cd/m^3 in copper-cadmium alloy production were reported from England. A report from a Japanese silver-cadmium alloy factory in 1967 showed an exposure level of 130 µg Cd/m^3 (Tsuchiya, 1967). Other reports from Belgian electronics, battery and cadmium factories in 1974 showed an exposure level of 31-34 µg Cd/m^3 (Lauwerys, 1974). The current occupational exposure levels of cadmium are between 10 and 50 µg Cd/m^3 in most countries (Stanescu, 1978).

Although inhalation is the major source of exposure to cadmium for industrial workers, ingestion of cadmium from hand contamination (mainly in workers who eat or smoke at the workplace) or from clearance of large particles deposited in the upper respiratory tract can also occur. Therefore all these factors should be considered in order to limit the exposure levels and to protect workers from excessive cadmium exposure.

Tobacco Smoking

Cadmium is known to accumulate in the leaves of tobacco plants and has been found in cigarettes at concentrations of 1 to 2 µg per cigarette. Using smoking machines, and standardized methods, 0.1 to 0.2 µg Cd per cigarette are found in mainstream smoke, and considerably higher concentrations (0.43 to 0.72 µg Cd/cigarette) in sidestream smoke (Menden, 1972). Smoking 20 cigarettes per day can result in the inhalation of 2 to 4 µg of cadmium depending on the amount of inhaled smoke (Lewis, 1972).

2.5 Measurement and Biological Monitoring

Although the determination of cadmium in biological materials at relatively high levels (parts per million and above) can be performed with few analytical problems, the measurement of cadmium at low concentrations in biological materials such as blood and urine is difficult. A number of critical reviews (O'Laughlin, 1976; Greenberg, 1979; Vahter, 1982; Piscator, 1979) have been published on analytical methods for cadmium in biological samples.

Atomic absorption spectrophotometry (AAS) is the most common method for the measurement of cadmium.

At levels above 5 µg/kg (0.005 ppm), cadmium can be accurately measured in food by the flameless AAS method. Even lower levels of cadmium in blood and urine have been measured by this method. However, interference by sodium salts and losses or contamination in the laboratory may cause major errors in estimation, if appropriate precautions are not taken (Piscator, 1979). Dithizone colorimetric methods and emission spectroscopic methods have also been used for cadmium determination, but these methods are less specific and less sensitive than AAS.

When exposure to cadmium is moderate and the critical organ concentration* has not yet been reached in the kidney the cadmium concentration in urine is believed to be related to the body burden of cadmium rather than to recent exposure to the metal. In the case of very high exposure to cadmium, urine cadmium levels may be influenced by current exposure as well as body burden. In persons not occupationally exposed to cadmium the level of cadmium in urine rarely exceed 2 µg/g creatinine. The level of cadmium in urine at which it is believed kidney dysfunction may occur is generally accepted to be above 10 µug/g creatinine. For more detail see section 4.2.1. In occupationally exposed persons the level of cadmium in blood is an indicator of the average intake during recent months but not of body burden.

Prolonged exposure to cadmium may cause renal dysfunction associated with proteinuria. The proteinuria is mainly due to an increased excretion of low molecular weight proteins (in the range of 10,000 - 30,000 Daltons). The measurement of β_2-microglobulin in urine has been used as an indication of this early kidney dysfunction (for more detail see section 4.2.1). β_2-microglobulin is, however, not stable in the urine and may, depending upon the urinary pH, break down in the bladder. Retinol-binding protein (α_2-microglobulin) has been proposed as a preferred indicator of tubular function because of its greater stability. Both proteins may be assessed by immunoprecipitation or

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* Critical Organ Concentration was defined as the mean concentration in the organ at the time any of its cells reaches critical concentration (Task Group on Metal Accumulation (TGMA) 1973). The critical concentration for a cell was defined by the TGMA as the concentration at which adverse functional changes, reversible or irreversible, occur in the cell.

radioimmunoassay techniques. More detailed information is available in sections 3.5 and 4.2.1.

Neutron activation analysis has been used successfully in a number of research projects for the measurement of cadmium *in vivo* in human liver and kidney (Vartsky, 1977) but this technique is not sensitive enough to measure cadmium in biological samples such as urine and blood. An elevated hepatic level of cadmium has been demonstrated in cadmium exposed workers and, in later studies, high enough sensitivity has been achieved to measure cadmium concentrations of 16 µg/g in liver and 1.8 µg/g in kidney. This method was also used to estimate the critical concentration of cadmium in the kidneys of cadmium-exposed workers in Belgium (Fletcher, 1982) and the U.S.A. (Ellis, 1982). This method involves sophisticated techniques which require special instrumentation. A recent paper by Ellis et al. (1984) has suggested that measurement of cadmium in liver is a more reliable indicator of body burden of cadmium than is the measurement of cadmium in kidney using neutron activation analysis, particularly if kidney dysfunction is present.

3. TOXICOKINETICS

Cadmium appears to be unique among non-essential metals in its pharmacokinetics and some of its toxicological effects in humans and other living organisms. It has an unusually long biological half-time in its target organs in humans. Following chronic exposure there may be a long lag period before signs of toxicity appear (Friberg, 1974). In such chronic low-level exposure cadmium is absorbed from the respiratory and gastrointestinal tracts and enters the blood. In blood cadmium is chiefly associated with the red blood cells and only a small portion is found in the plasma (Ulander, 1974). It mainly accumulates in the liver and kidney with small amounts in other tissues (Friberg et

al., 1979). Cadmium is transported from liver and lung to kidney where it accumulates more in the cortex than in the medulla (Tipton, 1963).

Cadmium compounds do not readily penetrate the blood brain barrier and, therefore, brain levels and the neurotoxic potential of cadmium are relatively small even in chronic exposures (T.G.M.A., 1973 p. 82)(Nogawa, 1975).

3.1 Absorption

The two main systems involved in the absorption of cadmium in humans are the respiratory and the gastrointestinal tracts. The absorption of cadmium compounds through the skin is negligible.

3.1.1 Respiratory Absorption

Cadmium intake by the respiratory system is an important route in industrial exposure. The pulmonary deposition, retention and absorption of cadmium are influenced by the physicochemical properties of the airborne cadmium at the time of exposure. The extent of deposition in the pulmonary tract compartments is a function of ventilation and particle size. Under normal conditions, cadmium-containing aerosols are deposited in the lungs and in the tracheobronchial tree in quantities related to particle size; lung deposition is about 50 percent for particles of 0.1 micrometer median mass diameter (MMD) ranging down to about 10 percent for particles with 5 micrometers MMD. Deposition in the nasopharyngeal tract increases as the MMD increases above 5 micrometers. The larger particles are cleared from the tracheobronchial region by mucociliary action to the gastrointestinal tract and this results in some gastrointestinal absorption. (Further detail can be found in section 6.1).

A portion of the material deposited in the respiratory system is assimilated directly into the blood and lymphatic systems. There are insufficient data available to determine the actual absorption of cadmium from the amount deposited in the respiratory tract, although theoretical calculations are available based on the tissue concentrations of cadmium in smokers (Friberg, 1974; Kjellstrom, 1979). The absorption of inhaled cadmium from the lung in humans is estimated to vary from 20 to 60 percent. Cadmium fumes and cadmium oxide deposited in the lung are rapidly translocated from the respiratory surface to the general circulation.

3.1.2 Gastrointestinal Absorption

The factors which control the absorption of toxic metals from the gastrointestinal tract are not well-defined. It is known that there are specific homeostatic mechanisms which control the absorption of essential metals such as iron, zinc and copper in humans. However, there is no evidence for such a control mechanism in the absorption of non-essential metals such as cadmium. The gastrointestinal absorption of cadmium occurs by a passive process. The usual gastrointestinal absorption of cadmium from cadmium salts is estimated to be about 6% of the ingested dose in humans (Friberg, 1974; Kjellstrom, 1979). A similar percentage absorption has been reported for cadmium from rice grown in polluted areas in Japan (Yamagata, 1975). This absorption pattern appears to be significantly influenced by the nutritional status of the individual. A Canadian study (Flanagan, 1978) on volunteers showed that the gastrointestinal absorption of cadmium salts was directly related to the serum ferritin levels or the iron store in the body. The absorption of cadmium increased markedly in persons with low serum ferritin levels. Because of the potential

high toxicity of cadmium, there are only a few studies in the literature involving voluntary human exposure to cadmium.

Studies on experimental animals have shown that newborn and young mammals can absorb more cadmium from the gastrointestinal tract than can adults (Kostial, 1979). Low dietary calcium and iron can also increase the absorption of cadmium in animals (Washko, 1974). In these respects cadmium behaves in a similar fashion to lead.

3.2 Tissue Deposition

After absorption from the lung or the gut, cadmium enters the general circulation and is transported to various tissues in the body. In experimental animal studies after a single IV dose 98-99% in the blood Cd^{2+} is found in the plasma and very little is bound to erythrocytes (Perry et al., 1970 cited in Webb, 1979). When repeated injections are given to animals the Cd^{2+} in the blood is localized predominatly in erythrocytes (Friberg 1952, Friberg, 1955 cited in Webb, 1979).

The average whole blood cadmium level is very low in persons not industrially exposed and is about 2 ng/ml or less in non-smokers and about 3-5 ng/ml in smokers. The data obtained from various countries by a WHO monitoring study (Vahter, 1982) are shown in Table 1. In exposed workers marked fluctuations in blood cadmium values are reported (10 to 70 ng/ml), depending on the time elapsed since the last exposure (Kjellstrom, 1978; Piscator, 1977). Although the blood cadmium concentration increases with exposure, in chronic exposure the blood levels remain much lower than the concentrations in liver and kidney. The biological half-time of cadmium in blood is estimated at 2.5 months (Kjellstrom, 1978)

which is similar to the observed value in cadmium workers after termination of a single high exposure (Piscator, 1977).

Autopsy studies have shown that in humans without any occupational exposure, cadmium deposited in liver and kidney constitutes about 50 to 60 percent of the total body burden. In occupationally-exposed people, appreciable amounts of cadmium are also found in the lung. Because of the long biological half-time in the human body (estimated to be greater than 10 years) cadmium accumulates in tissues with age (Friberg, 1974). In the general population, a higher body burden of cadmium in smokers as compared to non-smokers has also been confirmed by tissue analysis.

By examining human autopsy samples from Germany, Kemper and Bertrom (1979) have confirmed that cadmium concentration in liver increases continuously with age. In kidney, cadmium concentration increases progressively up to age 50-60 and then decreases. It is also known that the cadmium concentration in human kidney cortex can be estimated by multiplying the whole kidney cadmium concentration by 1.5 (Friberg, 1974). More recent research (Svartengren, 1984) has suggested that this factor should be reduced to 1.25. The mean concentrations of cadmium in the renal cortices of 50 year-old individuals (both smokers and non-smokers) without any known exposure have been reported from various countries and are shown in Table 2.

Reports (Friberg, 1974; Vahter, 1982) suggest that there are large variations in tissue levels of cadmium, in various countries, depending on the environmental cadmium levels. The highest reported values are from Japan while those from China and Sweden are the lowest. These data also show that the body burden and

hence the renal cortical cadmium levels are higher in smokers than in non-smokers in most of the countries (Vahter, 1982).

Animal experiments using different routes of exposure have all demonstrated that the largest amount of absorbed cadmium will initially be found in the liver. After exposure has ceased a slow translocation from liver to kidney takes place, most likely through the transport of hepatic cadmium-metallothionein (Cd-Mt) via the blood since circulating Cd-Mt complex has been demonstrated in the plasma of rats and mice after chronic cadmium exposure (Cherian et al.,1977; Goyer et al., 1978; Shaikh et al., 1979; Suzuki et al., 1982; Suzuki, 1981; Vander, Maille et al., 1979). Metallothionein (Mt) has been demonstrated in plasma one day after exposure to cadmium (Garvey, 1981). Metallothionein has also been found in the plasma and urine of cadmium-exposed humans (Nordberg et al., 1982; Tohyama et al., 1981; Tohyama et al., 1981; Chang et al., 1980; Suzuki et al., 1977). More detailed information about metallothionein is given in Section 3.2.1. The biological half-time of a single dose of cadmium was found to be 73 days in liver and 1,240 days in the kidney of the rat (Ellis, 1983). Therefore, after prolonged exposure, the kidney may eventually contain the highest concentration of cadmium, although the liver is the largest depot.

Cadmium levels in maternal blood, foetal cord blood and the placental tissues of pregnant American women have been reported. This study concluded that the mean levels of cadmium in maternal blood, cord blood and placental tissues of pregnant women who smoked were all higher than the mean levels of cadmium in the same tissues and blood of pregnant women who did not smoke. The cadmium levels in the maternal blood of smokers were significantly higher than levels of cadmium in the cord blood of their infants (Kuhnert, 1982).

Similar results of analysis of cadmium in placenta and in maternal and umbilical cord blood samples were also reported from Belgium (Lauwerys, 1978). These studies show that during pregnancy the placenta accumulates cadmium and thus the placenta may provide a partial barrier against transport of cadmium to the foetus, at least at low level cadmium exposure. In this regard cadmium differs from lead (Lauwerys, 1978) and methyl mercury (Clarkson, 1983) which are known to be passively transported to the foetus from the mother. However, no studies have been undertaken of the effects of high levels of cadmium exposure, such as those which occur in occupational exposure.

In workers exposed chronically to cadmium oxide dust and fumes, the concentrations of cadmium in both liver and kidney are generally higher than the values reported from a number of countries (Table 1) for the general population. However, in some occupationally-exposed persons (Friberg, 1974), the hepatic and renal cadmium levels are almost equivalent to the control values reported from certain parts of Japan where the environmental cadmium exposure is high. It has also been reported that cadmium levels in the renal cortex of certain cadmium workers who died of renal disease are even lower than the normal values. This may be due to loss of cadmium, from kidney, following renal damage. All these results on human tissue levels have been obtained from the analysis of cadmium in autopsied tissues.

3.2.1 Metallothionein

In mammals, a major cellular response of exposure to cadmium compounds is a large increase in tissue concentration of a sulfur-rich metal binding protein, known as metallothionein (Kagi, 1960). It is a low molecular weight protein (6,000 to 7,000 Daltons) with a high cysteine content (30%). Although it is normally found in low concentrations in the tissues of adult mammals, exposure to sublethal doses of cadmium, mercury, zinc and copper salts can induce its synthesis in various tissues. Spectroscopic studies on metallothionein reveal a unique polynuclear metal structure consisting of two distinct metal clusters with all the Cd^{2+} tetrahedrally co-ordinated to cysteine thiolate ligands (Boulanger, 1983).

High concentrations of zinc and copper are associated with metallothionein in the livers of term foetuses and newborn mammals. Normally, about 7 moles of metal per mole of protein are found in metallothionein. Since trace elements such as zinc are essential during rapid growth and development, the major biological role of metallothionein may be to store zinc, and probably copper, in the fetal-neonatal developmental stage in mammals (Webb, 1982; Panemangalore, 1983).

Animal experiments demonstrate that within a few hours following initial exposure, cadmium in blood is bound to albumin and other proteins with molecular weights higher than albumin. Cadmium in this form is taken up by the liver where it is incorporated into metallothionein. Nearly all the intracellular cadmium is bound to this protein, which may protect the cell organelles from the potential toxic effects of the cadmium ion. The cadmium-metallothionein complex is released into the blood, filters through the kidney glomerulus and is reabsorbed by the tubules where it accumulates. Webb and Etienne (1977), Fowler and Nordberg (1978) and

Squibb (1979) have suggested that the cadmium ion released from the lysosomal breakdown of cadmium-metallothionein induces the renal biosynthesis of metallothionein (Suzuki and Yamamura, 1980) and may also cause renal dysfunction. According to this theory, the nephrotoxic action of cadmium is the direct consequence of its mode of transport from the liver to the kidney and its metabolism in the kidney.

An alternate theory is that extracellular cadmium-metallothionein is directly nephrotoxic (Cherian, 1976; Cherian and Goyer, 1978). It has been shown experimentally that extracellular cadmium-metallothionein is very toxic to renal tubular cells. In experimental animals, the effects on renal tubular cells of a single injection of cadmium complexed to metallothionein were very dramatic, and resulted in tubular necrosis within a few hours. Injection of a similar dose of cadmium, as cadmium chloride, had no effect on the kidney, nor did the injection of a similar dose of zinc-metallothionein. These results were due to the dispositional differences of metals in the body after administration of different forms. When cadmium chloride was injected into experimental animals, most of the cadmium was recovered in the liver, and the pattern of deposition was similar when cadmium salts were ingested. Only a small fraction of the injected cadmium appeared in the urine. However, when cadmium-metallothionein was injected a major fraction was deposited in the kidney and was accompanied by renal tubular cell injury. Subsequently there was a loss of cadmium from the kidney and the appearance of cadmium in the urine.

Although the direct extrapolation of these results to chronic cadmium exposure is difficult, these studies show that the extracellular cadmium-metallothionein complex may be the nephrotoxin in cadmium-induced nephrotoxicity (Cherian, 1976). However, the mechanism of cadmium-induced nephrotoxicity is not yet clearly understood.

The induced synthesis of metallothionein by cadmium and its high specificity for intracellular binding of cadmium are particularly interesting because this protein appears to modify the pathological effects of exposure to cadmium while intracellular, and may itself be toxic when the cadmium-metallothionein complex becomes extracellular (Cherian, 1978). The very long biological half-time of cadmium in humans may be due to the binding of cadmium in various organs, including liver and kidney, to an intracellular storage protein like metallothionein.

Although a number of indicators of renal dysfunction are used for evaluation of cadmium toxicity, none of them can be considered as specific indicators of metal exposure. Urinary metallothionein levels may be a more specific index of metal-induced renal disease than commonly used parameters such as proteinuria, glycosuria and aciduria, because metallothionein excretion is closely related to cadmium exposure (Piscator et al., 1977). However, the methods of estimation of metallothionein were not sensitive enough to measure the levels in urine until a radioimmunoassay for metallothionein was developed (Vander-Mallie, 1979). Although this method is difficult to standardize for the analysis of biological samples, preliminary data on urine from cadmium workers suggest that the urinary metallothionein level is closely related to both hepatic and renal cadmium content before the onset of renal dysfunction (Chang, 1980; Tohyama, 1981). A correlation between urinary excretion of cadmium and of metallothionein, in cadmium workers, has also been suggested (Tohyama, 1981). A recent study of cadmium exposed workers showed an excellent correlation between Cd-U and Mt-U in a number of subgroups among these workers (currently exposed to Cd; removed from Cd exposure; normal or abnormal renal function) (Roels, 1983). One possible advantage of Mt-U over Cd-U in biological monitoring is that the determination of Mt-U is not

influenced by external contamination of the urinary sample as easily as the determination of Cd-U (Lauwerys, 1982). Because of the interfering substances in urine and plasma, the radioimmunoassay should be properly standardized with regard to internal and external quality control before such studies in occupationally-exposed people are undertaken.

3.3 Excretion

Only a small part of the cadmium absorbed during long-term low level exposure is excreted. This results in the slow accumulation of cadmium in the body which is mainly deposited in the liver and kidn y. In animal experiments, depending to some extent on the dose levels used, the amount excreted daily accounted for 0.01 - 0.02% of the estimated body burden of cadmium (Nordberg and Piscator, 1972). The average normal excretion of cadmium in human urine is less than 5 µg/day (Lauwerys, 1982; Kowal, 1983) compared with an estimated daily intake of 10-80 µg in western countries of which less than 10% is absorbed. (The usual estimate of gastrointestinal absorption is 6%).

The urinary excretion of cadmium may increase with age and also after renal damage whether the renal damage is due to exposure to cadmium or some other unrelated cause. In workers with long-term exposure to relatively low concentrations of cadmium oxide dust, urinary cadmium excretion did not usually exceed 10 µg/g creatinine in those with normal kidney function, whereas workers with tubular proteinuria excreted considerably larger amounts of cadmium. In cadmium workers from Belgium, values as high as 247 µg Cd/g creatinine have been reported (Lauwerys, 1974; Chang, 1980). Renal tubular dysfunction may thus result in increased urinary excretion of cadmium and is normally accompanied by proteinuria and increased metallothionein excretion (Chang, 1980). Thus, in workers with normal kidney

function, urinary excretion of cadmium can be used as an indicator of cadmium exposure in chronic low level exposures (Bernard, 1976).

In workers with short-term, high level exposure to cadmium oxide dust or fumes, the urinary excretion of cadmium may sometimes be high without any major changes in renal function (Piscator, 1977). In these cases, the increased urinary cadmium excretion is a reflection of the recent exposure rather than increased body burden or renal damage. These workers also have a relatively high blood cadmium concentration. The increased urinary excretion observed in cases with renal damage may explain the low levels of cadmium in the kidneys of autopsied workers with severe morphological renal changes (Friberg, 1974; Friberg, 1979).

Since renal dysfunction is not observed normally in cadmium workers whose urinary cadmium does not regularly exceed 10 µg/g creatinine (Roels, 1981), determination of urinary cadmium is considered a useful indicator for monitoring excessive exposure to cadmium in the workplace. The biological parameters used to determine renal dysfunction due to cadmium toxicity are proteinuria and urinary β_2-microglobulin excretion. Some of the values reported in the literature in control subjects and cadmium workers with and without renal damage are shown in Table 3, along with the history of exposure and cadmium levels in urine and blood.

3.4 Biological Half-Time

Cadmium has an extremely long biological half-time, 10 to 30 years, in humans (Friberg, 1974). There is considerable difference of opinion with regard to the appropriate model for accumulation of cadmium in different organs, including kidney. In human volunteer studies, using radioactive cadmium, biological half-times of 100 to 200 days were obtained when short-time

measurements were made (Yamagata, 1975; Flanagan, 1978). However, in a similar study, a biological half-time of 26.7 years was obtained after measurements over 3 years (Shaikh, 1980). Since very little cadmium is excreted from the body during continuous low level exposure, both measurements and mathematical models favour a very long biological half-time (~10 years) for cadmium in humans.

3.5 Significance of Blood and Urine Cadmium Concentrations

There are some uncertainties with regard to the precise relationship between cadmium exposure, cadmium body burden, detriment to health and cadmium concentration in blood and urine. There are, however, adequate data to support the use of blood and urine cadmium measurements in exposed workers as indicators of occupational exposure to and body burden of the cadmium.

The total amount of cadmium absorbed or the total body burden can be estimated by biological monitoring and this data used to prevent over-exposure to cadmium. Biological monitoring does not, however, indicate the source of the cadmium retained in the body. Biological monitoring should be used in connection with, and as a supplement to, air monitoring.

3.5.1. Urine Cadmium Concentrations

When exposure to cadmium is moderate and the body burden has not yet reached the critical level (the level at which there is evidence that kidney dysfunction may develop), cadmium concentration in urine is believed to represent the body burden of cadmium rather than recent exposure. This theory is supported by a Belgian study (Roels, 1981). In this study *in vivo* measurements of cadmium in kidney and liver were made. In those workers whose kidney and liver cadmium levels were above the

detection limit but in whom no indication of kidney dysfunction was found, cadmium concentration in urine was significantly correlated with the cadmium content measured in kidney and liver.

In the case of very high exposure to cadmium, urine cadmium levels, after a period of time, may be influenced by current exposure as well as body burden (Lauwerys, 1979).

When cadmium exposure is not excessive and the critical level of cadmium in the renal cortex has not been reached, the cadmium concentration in urine rarely exceeds 10 µg/g creatinine.

3.5.2. Blood Cadmium Concentrations

Blood levels of cadmium reflect relatively recent exposure to cadmium. The half-time of cadmium in blood is believed to be about two and one-half months. Following the start of exposure, cadmium concentration in blood increases during the first 4-5 months and then levels off. The value of the plateau level seems to be proportional to the exposure intensity (Lauwerys, 1979; Kjellstrom, 1979) and correlated with the average cadmium exposure during the preceeding 2-3 months. A survey of Belgian workers (Roels 1981) confirmed the finding that cadmium levels in blood reflect the cadmium exposure of the 2 to 3 month time period preceeding the sample. In occupationally-exposed persons, the cadmium level in blood is a good indicator of the average intake during recent months but not of body burden.

4. TOXICOLOGY

In humans, the adverse health effects of cadmium may arise from either acute or chronic exposure. The acute toxic effects of cadmium in humans are based upon

reports of a few industrial workers who had acute cadmium exposure and upon certain accidental exposures (Patwardhan, 1976; Beton, 1966).

4.1 Acute Effects

The acute toxic manifestations observed in humans are chemical pneumonitis following inhalation of high levels of cadmium oxide fumes, and gastrointestinal disturbances following the inges intensity (Lauwerys, 1979; Kjellstrom, 1979) and correlated with the average cadmium exposure during the preceeding 2-3 months. A survey of Belgian workers (Roels 1981) confirmed the finding that cadmium levels in blood reflect the cadmium exposumium compounds by various routes.

4.1.1 Respiratory Effects

The most serious acute effect from a cadmium exposure in industry results from exposure to cadmium oxide fumes. Exposure to as little as 2-3 mg of c[a]dmium oxide fumes per cubic meter has produced a characteristic clinical picture. There is minimal or no discomfort at the time of exposure and a lethal exposure is possible without warning (Patwardhan, 1976).

Symptoms usually appear 4 to 10 hours following exposure when dyspnea, cough and tightness in the chest develop. Substernal chest pain and a burning sensation in the chest, aggravated by coughing, may be experienced. A flu-like syndrome may develop, not unlike metal fume fever with chills, fever and muscular pain in the back and limbs. Acute pulmonary edema may develop in 24 hours, depending on the severity of the exposure.

In less severe exposures, symptoms may resolve within a week; but in more severe exposures, dyspnea may be progressive and associated with wheezing and haemoptysis. In some severe exposures, death has

occurred within one week. Residual changes, such as interstitial pulmonary fibrosis, have been attributed to acute inhalation exposure. However, the question of whether a non-fatal acute exposure can produce long-term effects in human beings has not been properly studied. One case report showed renal necrosis after acute cadmium fume poisoning (Beton, 1966). Acute toxicity due to cadmium dust exposure can also produce respiratory toxicity, but is less severe than that due to cadmium oxide fumes.

Human data regarding a dose-response relationship for acute cadmium fume exposures are scarce. On the basis of a few published cases (Patwardhan, 1976; Beton, 1966), it has been estimated that the lethal concentration of thermally generated cadmium oxide fumes*[1]. For an 8 hour exposure around 5 mg/m^3 can be considered lethal for cadmium oxide fumes and an exposure of 0.5 mg/m^3 for an 8-hour exposure will result in clinically evident symptoms such as pneumonitis (Lauwerys, 1977; WHO, 1980). The data necessary for similar calculations of the effects of cadmium dust*[2] are not available. From experimental data in rabbits using cadmium dust in which 95% of the particles were 5 microns or less in size, a lethal concentration value of about 17 mg/m^3 for 8 hours exposure in humans has been calculated (Lewis, 1972).

Smith (1976) found mild and moderate interstitial

Particle	Size in μ	
*[1]Fumes	0.001-1.0	Small solid particles created by condensation from vapour state, especially volatized metals as in welding. Fumes tend to coalesce into larger particles as the small fume particles collide.
*[2]Dust (Air-borne)	0.1-30.0	Generated by pulverization or crushing of solids. Typical examples are rock, metal, wood and coal dust. Particles may be up to 300-400 μ but those above 20-30 μ usually do not remain air-borne.

fibrosis in an occupational study group with a history of high exposure to airborne cadmium (levels ~0.2 mg/m^3). Associated impairment in pulmonary function, as shown by a significantly decreased forced vital capacity (FVC) was also observed in comparing data obtained from low exposure co-workers and unexposed control subjects matched for age, smoking status and other pertinent characteristics. According to Wilcox (1973), 0.5 mg/m^3 in workroom air has been associated with mild pneumonitis. If a worker is not exposed to a concentration greater than 0.25 mg cadmium/m^3 air for a period not exceeding one hour even a mild form of pneumonitis should not develop (WHO, 1980).

Acute exposure to cadmium fumes can usually be controlled because the conditions which will generate cadmium fumes can be predicted. However, cases of acute pneumonitis, with sometimes fatal outcome, are reported in the world literature each year, mainly among welders who are not properly instructed in, or those who have not followed, appropriate preventive measures (Lauwerys, 1978).

4.1.2 Gastrointestinal Effects of Cadmium

In earlier reports, gastrointestinal effects were common findings in acute cadmium poisoning due to the ingestion of food contaminated with cadmium. The contamination is usually caused by storage of food in cadmium plated containers, cans, etc., or solubilization of cadmium from pottery glazes. In most countries, the outbreaks of food poisoning due to cadmium have become less frequent since the use of cadmium has been prohibited in utensils for cooking and storing food. Some recent reports (Baker, 1961; Nordberg, 1973), however, indicate that this problem may still exist.

Cadmium is a powerful emetic. The highest no-effect level of cadmium administered as a single oral dose to

man is estimated at 3 mg. Estimates for the lethal dose range from 350 - 8,900 mg. The concentration in water that induces vomiting is about 15 mg/l (Lauwerys, 1977). The ingestion of cadmium salts may induce salivation, choking attacks, persistent vomiting, abdominal pains, tenesmus diarrhea, vertigo, and loss of consciousness. Catarrhal and ulcerative gastroenteritis, congestion, pulmonary infarcts, and subdural hemorrhages may be found at necropsy.

In workers exposed to cadmium dust of a large particle size, gastrointestinal effects may be observed due to clearance of the particles from the respiratory to the gastrointestinal tract.

4.1.3 Other Acute Toxic Effects

Both liver (Wisniewska-Knypl, 1971) and kidney damage (Beton, 1966) have been noted in case reports of acute exposures to high concentrations of cadmium oxide fumes. These effects are uncommon in short term low-level exposures to cadmium. A number of experimental studies on animals injected with cadmium compounds found acute toxic effects such as testicular necrosis (Parizek, 1956), changes in blood pressure (Dalhamn and Friberg, 1954) and changes in the nervous system (Gabbiani, 1966). However, there are no reports of similar effects in humans after acute exposure to cadmium. No reports of injection of humans with cadmium compounds have been found in the literature.

4.2 Chronic Effects

The predominant effects of low level chronic exposure to cadmium in workers are renal and pulmonary damage. The relative severity of renal versus lung damage is dependent on the intensity of the exposure (and presumably also on variations in individual susceptibility) so that with more intense exposure

relatively more lung damage is seen, whereas with low exposures for very long time periods only renal damage may develop. There are also limited reports of the toxic effects of cadmium on bone, liver and the cardiovascular system. The relationship between exposure to cadmium and carcinogenesis is controversial (see Section 4.2.5).

4.2.1 Renal Effects

A number of toxicological studies (Friberg, 1974; Nordberg, 1976) have shown that the kidney is the critical organ in long-term, low-level exposure to cadmium. In continuous exposure, after absorption from the lung, cadmium accumulates in the renal cortex where it produces both morphological and functional changes. Although the kidney seems to have some tolerance for the toxic effect of cadmium, both animal studies and post-mortem examinations of cadmium-affected workers suggest that renal damage may occur when a critical level of cadmium in kidney cortex has been reached (Smith, 1960; Baaser, 1952). In a number of reports the critical concentration in kidney cortex has been suggested to be between 200 and 300mg Cd/kg (Lauwerys, 1979; Nordberg, 1976; Roels, 1976; WHO, 1980; WHO, 1977). However, due to the existence of individual biological variability, it is possible that the renal cortical-cadmium level in all cadmium workers may not rise to this level before the onset of renal dysfunction.

The early reports on cadmium induced renal dysfunction were published from Sweden (Friberg, 1948). Friberg investigated a large group of Swedish workers exposed to cadmium oxide dust in an alkaline nickel-cadmium accumulator factory and showed that prolonged exposure to cadmium resulted in renal damage, characterized by clinical proteinuria. Renal disease was observed in workers who had been exposed to cadmium for more than eight years. Further extensive studies (Adams, 1969;

Butler, 1962; Friberg, 1950; Kazantzis, 1963; Potts, 1965) in alkaline accumulator factories in Germany, England and France also revealed a high prevalence of proteinuria in cadmium workers. It was concluded that not only cadmium oxide dust, but also cadmium oxide fumes and cadmium stearate exposures may cause proteinuria in workers.

Follow-up studies (Friberg, 1950; Bonnell, 1959) of cadmium-exposed individuals suggest that the first sign of chronic cadmium poisoning may occur after a long latent period, sometimes after the cessation of exposure to cadmium. This finding is probably due to the long biological half-time of cadmium in humans, the movement of cadmium from the liver to the kidney and accumulation of cadmium in the kidney with time.

The characteristic feature of cadmium-induced renal effects is impairment of the re-absorptive function of the proximal tubules. Proteinuria produced in this manner is mainly due to a low molecular weight proteinuria, similar to that in the Fanconi Syndrome.

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plasma and are normally filtered through the glomerular membrane with subsequent reabsorption from the proximal tubules.

The urinary proteins in cadmium workers have been characterized by both electrophoresis and chemical analysis (Piscator, 1962). In this study all the cadmium workers with more than 15 years of excessive exposure had an increased urinary protein excretion (~250 mg/day), the degree of proteinuria being related to both the level and the duration of exposure. The electrophoretic pattern was characterized by a low albumin content and relatively large microglobulin fractions. In most of the cases with over 400 mg proteinuria per day, a distinct β peak was present and was later identified as β_2-microglobulin (Piscator, 1966). The urinary excretion of low molecular weight proteins (10,000 to 30,000 Daltons) was correlated with the excretion of total protein. Because of these findings, β_2-microglobulin has been used as an indicator of proximal tubular dysfunction, especially in excessive cadmium exposure (Piscator, 1977). β_2-microglobulin, is however not stable in the urine and may, depending upon the urinary pH, break down in the bladder. Retinol-binding protein (α_2-microglobulin) has been proposed as a preferred indicator of tubular function because of its greater stability. Both proteins may be assessed by immunoprecipitation or radioimmunoassay techniques.

The incidence of proteinuria in workers exposed to cadmium oxide fumes and dust from 8 to 30 years in an alkaline accumulator factory was investigated by Smith and Kench (1957). The incidence of increased proteinuria was greater in workers exposed to fumes (60%) and in those inhaling dust (20%) compared with the control group (5%). Both aminoaciduria and glucosuria may occur at a later stage and have also been reported in workers exposed to cadmium oxide dust (Bonnell, 1959; Clarkson, 1956). Adams (1969) found that workers with

proteinuria had some reduction in creatinine clearance with corresponding elevation of the serum creatinine. These exposed workers also showed an increased urinary excretion of uric acid, calcium and phosphate and developed renal calculi.

Once proteinuria is established in workers, it persists even after retirement or change of employment (Adams, 1969). Kazantzis (1979) reported that serious clinical effects, such as renal calculus formation and osteomalacia, may develop several years after renal tubular dysfunction has been discovered in workers. These findings are in agreement with previous observations (Friberg, 1952)..Osteo malacia is rarely reported in recent literature. There is some suggestion that dietary deficiency as well as proteinuria may have contributed to the cases of osteo malacia reported in earlier literature.

Studies (Lauwerys, 1974; Lauwerys, 1979) on Belgian workers who were exposed mainly to cadmium oxide dust showed that the prevalence of renal lesions was related to the duration of exposure to cadmium. The proteinuria was correlated with both urinary and blood cadmium levels. In the group exposed to cadmium for more than 20 years, a large proportion of workers (68%) had signs of kidney damage. Analysis of urinary proteins in these workers showed that cadmium-exposed workers with renal lesions excreted not only a larger amount of low molecular weight proteins such as lysozyme and β_2-microglobulin but also a larger amount of high molecular weight proteins such as albumin and transferrin. These results suggest that excessive exposure to cadmium can reduce both the re-absorption of low molecular weight proteins by the renal proximal tubules and also the integrity of the glomerular membrane with the excretion of high molecular weight proteins. The subjects with proteinuria had a urinary cadmium concentration higher than 10 µg/g creatinine.

Renal clearance studies of plasma proteins in the cadmium-exposed workers also showed both tubular and glomerular impairment (Bernard, 1979). The types of proteinuria may differ depending on the level and duration of exposure.

A detailed study of β_2-microglobulin urine levels and past airborne concentration of cadmium showed about a 19% prevalence rate of abnormal levels of urinary β_2-microglobulin (~290 µg/L) in alkaline battery factory workers (Kjellstrom, 1977). These results were obtained in workers exposed to a level of about 50 µg Cd/m^3 for 10 to 15 years and were in agreement with the calculation by Friberg in 1974. Friberg had concluded that an occupational exposure of 25 µg Cd/m^3 for 10 years could cause accumulation of cadmium in the kidney cortex up to the critical concentration.

In another study of 11 workers exposed to very high concentrations of cadmium, Lauwerys (1979) has estimated that an integrated exposure to 1500 to 3000 µg Cd/m^3 years leads to kidney disturbances. These results also suggested that workers whose exposure is such that cadmium in urine never exceeds 10 µg Cd/g creatinine will not develop kidney dysfunction. Based on these data, the Belgian research group have proposed a tentative biological threshold of 10 µg Cd/g urinary creatinine for adult males occupationally exposed to cadmium compounds (Lauwerys, 1977). This no-effect level, however, may not necessarily apply to other groups of the general population such as children or women after menopause, whose sensitivity to cadmium may be different.

The evaluation of renal function in workers removed from cadmium exposure indicates that cadmium-induced renal dysfunction is not reversible even after the exposure ceases. In a follow-up study of cadmium-exposed workers over a period of twenty years, Piscator (1983) showed

that once tubular dysfunction is established it is irreversible. In this study renal dysfunction was characterized as increased proteinuria (~50 mg/L) or increased excretion of β_2-microglobulin (~200 µg/g creatinine). This study also indicated that the development of renal dysfunction may be a multi-stage process. The initial stage is characterized by an increased excretion of low molecular weight proteins such as β_2-microglobulin and ribonuclease with a slight decrease in glomerular filtration rate. After a period of several years there may be a relatively sharp increase in excretion of total proteins and a further decrease in glomerular filtration rate.

The formation of renal stones has been a common feature in Swedish cadmium workers (Friberg, 1950; Ahlmark, 1961). About 44% of workers exposed to cadmium dust for more than 15 years had a history of renal stones, composed of basic calcium phosphate. The formation of such stones suggested a disturbance of the metabolism of calcium and phosphorus. A higher incidence of renal stones in men without any proteinuria indicates that changes in calcium re-absorption may occur earlier than that of protein re-absorption (Axelsson, 1963).

Determination of the cadmium concentration in kidney can provide an accurate measure of lifetime accumulation of cadmium. In a recent study (Ellis, 1983) attempts were made to evaluate the biological indicators of body burden and direct <u>in vivo</u> measurement of cadmium in kidney and liver by neutron capture gamma ray analysis in control subjects and cadmium workers. In general, both blood and urinary levels of cadmium were useful as indicators of cadmium exposure and correlations between blood and urinary cadmium and levels of cadmium in tissues in workers as a group were reported (Ellis, 1983). However, they did not find a good correlation between these biological monitors and body burden of cadmium for individual workers, particularly not for

those with renal dysfunction. This is not unexpected because with sufficiently high exposures, the cadmium binding sites in kidney can be saturated and then the urinary cadmium levels will be influenced more by recent exposures than by body burden.

On a group basis, the excretion of metallothionein and cadmium in urine of cadmium-exposed workers also appeared to be related to the levels of cadmium in both liver and kidney (Tohyama, 1981).

As the kidney is the critical organ in long-term exposure to cadmium, it is important to estimate the threshold exposure level below which there will be no detectable kidney dysfunction. Lack of data on workplace exposure levels and the renal content of cadmium in exposed workers make it difficult to evaluate the dose-response relationship of cadmium induced renal dysfunction in humans.

Estimation of the threshold effect level has been attempted by several investigators (Friberg, 1974; Lauwerys, 1977; Kjellstrom, 1977). Some of these estimations are based on direct evaluation of the no-effect exposures or the no-response exposures of cadmium by inhalation and a comparison of these values with the current industrial exposure levels. Lauwerys (1977) has estimated that an occupational exposure of 20 µg Cd/m^3 for 40 hours per week during 20 years would approach the critical organ concentration. Kjellstrom (1977) concluded that 6 to 12 years of exposure to 50 µg Cd/m^3 induces a functional response in about 20% of the population. A WHO Task Group (1977) estimated that exposure to dust containing about 50 µg Cd/m^3 of air for 10 to 20 years is associated with an increased risk of the development of renal tubular dysfunction.

Friberg (1974) used a different approach to calculate the threshold levels based on an estimation of the critical concentration of cadmium in the renal cortex (about 200 ppm). Assuming the subject is not occupationally exposed and considering only the respiratory intake, the pulmonary absorption rate and the estimated biological half-time in years, it can be calculated that with an exposure time of 50 years ambient air concentrations between 1 and 2 $\mu g/m^3$ may be sufficient to reach an estimated critical renal cortex level of 200 µg/g if the biological half-time is 38 years. (Table 4.2.1 #1).

Table 4.2.1 #1

Necessary Cadmium Concentration ($\mu g/m^3$) in Ambient Air to Reach Critical Cadmium Concentration (200 µg/g Wet Weight) in Kidney Cortex under Different Absorption, Excretion, and Exposure Time Alternatives (Ventilation = 20 m^3/24 hr).

Pulmonary absorption %	Exposure time in years	Biological half-time in years (39)	(19)	(9.5)
25	10	7.2	7.8	9.3
	25	3.3	4.0	5.7
	50	2.0	2.9	4.9
50	10	3.6	3.9	4.7
	25	1.7	2.0	2.9
	50	1.0	1.5	2.5

If a biological half-time of 9.5 years is assumed, an ambient air concentration of 2.5 to 4.9 $\mu g/m^3$ would be required to reach the same renal cortical level (Friberg, 1974). It was calculated that an occupational exposure to 30 $\mu g\ Cd/m^3$ (Ventilation: 10 m^3 during an 8-hour work day, 225 workdays per year) for 10 years could increase the renal deposition of cadmium to a critical concentration level. In this model, (Friberg, 1974) the variations in kidney weight and caloric intake with age are also considered.

A WHO Task Group (1980) suggests that, even assuming a negligible intake of cadmium by ingestion, the level of cadmium dust or cadmium oxide fumes should be kept below 20 $\mu g/m^3$ in order to prevent an increased prevalence of proteinuria in long-term cadmium exposure (see Table 5).

4.2.2. Respiratory Effects

In industrial workers repeatedly exposed to cadmium various types of lung disturbances have been reported.

Friberg (1974) reviewed the earlier studies on the chronic respiratory effects of cadmium compounds in humans. The most commonly reported pulmonary effect of chronic cadmium inhalation in man was emphysema, arising after several years of occupational exposure. Studies

on Swedish workers exposed to cadmium oxide dust showed shortness of breath and impaired lung function such as an increased residual capacity in relation to total lung capacity (Friberg, 1950; Friberg, 1948). No dose-response effects were calculated from these studies because of lack of data on the air levels of cadmium and additional exposures to nickel graphite dust in these workers.

Emphysema and other respiratory effects were also reported from Germany by Baader (1952) who studied workers exposed to cadmium oxide dust. Six out of eight exposed workers in this study suffered from emphysema, detected by clinical and radiological examinations. Workers exposed to cadmium in the production of cadmium pigments (Kazantzis, 1963) showed reduced lung function tests and mild obstructive lung disease.

British researchers (Adams, 1969; Bonnell, 1959; Kazantzis, 1963) have published several reports on chronic cadmium poisoning in humans exposed to cadmium oxide fumes in casting copper cadmium alloys. A prominent finding was emphysema. The respiratory function tests in exposed groups showed a greater deterioration with increasing age than in the control group. Tsuchiya (1967) examined Japanese workers exposed to cadmium fumes while smelting alloys of silver and cadmium and observed no abnormalities on chest x-ray or lung function tests.

In an *in vitro* study (Chowdhurdy, 1976) it was reported that cadmium, unlike other metals (iron, mercury, nickel, lead and zinc) caused a dose-related reduction in the α_1-antitrypsin content of human plasma and its trypsin inhibitory capacity. It was thought that this *in vitro* observation might provide a potential

explanation for the emphysema reported in some industrial workers exposed to cadmium. However, further work (Bernard, 1977) on the measurement of α_1-antitrypsin levels in plasma and its trypsin inhibitory capacity in cadmium workers and control groups failed to show any difference, although the cadmium workers had renal damage. No relationship was found between α_1-antitrypsin and the cadmium content of plasma. It should be mentioned that emphysema and other respiratory effects are not usually reported in workers exposed chronically to cadmium in Belgium (Lauwerys, 1974; Stanescu, 1978) and Japan (Tsuchiya, 1967). Therefore, it is difficult to attribute a direct role for α_1-antitrypsin inhibition in the etiology of cadmium-induced lung changes from these studies.

In 1974, Lauwerys et al. reported on a cross-sectional study of Belgian workers. A group of 150 workers exposed to cadmium and a control group matched for age, height, smoking habits and duration of work in the same factory were examined in an attempt to determine the extent and prevalence of lung and kidney disease. The highest respirable cadmium dust concentrations recorded in these four factories were 4, 88, 21 and 65 $\mu g/m^3$, respectively. The conclusion of the study was that only mild obstructive lung disease was found even among groups of workers exposed for more than 20 years to cadmium oxide dust and fumes. The cadmium-exposed group when compared with the control group showed a mild but statistically significant reduction in lung function tests. There were no significant differences detected

between the control and the cadmium-exposed workers with regard to chest x-ray findings or clinical symptoms of chest disease.

A second study, based on the same population, was carried out (Stanescu et al. 1977). Eighteen workers exposed to cadmium dust and fumes for an average of 32 years were compared with a control group of 20 non-exposed workers matched for age, weight, height, smoking habits and socio-economic status. The authors concluded that they were unable to find evidence of emphysema among the cadmium-exposed workers. In the absence of acute overexposure to cadmium fume, only a mild form of obstructive lung disease was found among some workers chronically exposed to cadmium.

Smith et al. (1976) investigated three groups of workers. The high (n=17) and low (n=12) cadmium exposure groups were selected from workers at a cadmium production plant in Denver, Colorado. The high exposure group included all those who had worked for six years or more in plant areas with airborne cadmium concentrations commonly greater than 0.2 mg/m^3 and a record of submitting a urine sample containing more than 50 µg cadmium per litre at least once. The control group (n=18) was selected from the maintenance staff of the University of Colorado Medical Centre. The control and low-exposure groups were matched to the high exposure group for age and cigarette smoking status. Clinical histories, pulmonary function tests, blood gases and postero-anterior chest films as well as cadmium air exposure and urine values were recorded for each subject.

The high cadmium exposure group had significantly lower forced vital capacities (FVC) relative to the low exposure group. The age and height adjusted pulmonary function values for the control subjects (not exposed to cadmium) were intermediate between the two in-plant

groups. Among the high cadmium exposure group, review of the chest x-rays identified 3 subjects with mild fibrosis and 2 subjects with moderate fibrosis. The findings in this study are suggestive of a mild restrictive pulmonary function defect in the workers exposed to cadmium.

Although emphysema has been frequently reported in earlier studies on cadmium workers, it has not always been detected in recent studies on cadmium workers. The possibility remains, however, that emphysema may develop after one or more episodes of acute pneumonitis.

Cross-sectional reports on actively employed cadmium workers suggest that in the absence of acute over-exposure, the functional changes induced by cadmium in the lungs are mild. However, the study populations may have constituted a selected group of workers who suffered less adverse effects than would have been found among workers who had retired or resigned. The findings may therefore represent a considerable understatement of the reality.

4.2.3. Effects on Bone

The pathological changes in bone during chronic cadmium poisoning are controversial. There are reports from France (Nicaud, 1942) and Britain (Potts, 1965) of bone changes in workers chronically exposed to cadmium. On the other hand, studies investigating chronic poisoning in cadmium workers in Sweden have failed to show even a single case of a bone lesion (Friberg, 1950). Some of the cadmium workers in an alkaline accumulator factory in France (Nicaud, 1942) showed iron-deficiency anaemia and severe osteoporosis with pseudo-fractures of the bones. Adams (1969) reported one case of a worker in the alkaline battery industry who developed osteomalacia with multiple fractures after 36 years of exposure to cadmium. Pujol also reported signs of osteomalacia in

one worker who had been exposed to cadmium fumes for 16 years (Pujol, 1970). Another study (Kazantzis, 1979) showed that one worker developed osteomalacia after twelve years of renal tubular defect attributed to occupational exposure to cadmium.

There are a number of reports (Adams, 1969; Kazantzis, 1979; Scott, 1981) on the increased excretion of calcium and phosphate in cadmium workers. Based on these findings, it can be concluded that there may not be a direct effect of cadmium on bone tissue, but the effects may be secondary to renal tubular dysfunction and changes in calcium, vitamin D and phosphate metabolism.

Decalcification of bone was a prominent feature of 'Itai-Itai' disease in the Jinzu River basin in Japan and this was first diagnosed as a vitamin D-resistant osteomalacia (Friberg, 1974; Nogawa, 1973; Shigegatsu, 1979). Even though excessive cadmium intake in food was a major factor in the development of this disease, other factors such as deficiency of calcium and vitamin D might have significantly contributed to the extensive osteoporosis. Cases of osteomalacia were not detected in cadmium-polluted areas other than the Jinzu River basin despite a high prevalance of renal tubular dysfunction in all these areas. It would appear, therefore, that when osteomalacia is observed in cadmium poisoning it is likely that nutritional deficiencies have also been present.

4.2.4. Cardiovascular Effects and Hypertension

Several epidemiological studies have focussed on the possible relationship between the prevalence of cardiovascular disease and exposure to cadmium. Although a correlation between the air cadmium concentrations in 28 American cities and death rates from hypertension and atherosclerotic heart diseases was reported (Carroll, 1966), later studies (Hine, 1973;

Hunt, 1971) did not confirm this relationship.

Since cigarette smoking is a contributory factor in the development of cardiovascular diseases and is also a source of exposure to cadmium, smoking habits should be considered in determining the relationship between cadmium and hypertension. A comparative study on blood cadmium levels in hypertensive and normotensive patients matched for age and sex but not taking smoking habits into account showed no significant difference in blood cadmium levels although the blood-cadmium level was significantly higher in smokers as compared with non-smokers (Beevers, 1976).

It has been argued that if cadmium were an important factor in the etiology of hypertension workers exposed to cadmium would show a higher incidence of hypertension than other control groups. This has not been a consistent finding in workers chronically exposed to cadmium compounds. Moreover, no relationship between cadmium levels and hypertension has been observed in persons living in polluted areas in Japan (Shigegatsu, 1979). Although experimental animal studies (Kopp, 1982; Kopp, 1983) indicate a direct effect of cadmium on cardiovascular diseases (including hypertension), there is as yet no firm evidence that cadmium, either in acute toxic exposures or chronic low-level exposures, plays a major role in the development of hypertension in humans.

4.2.5. Mutagenic and Carcinogenic Effects

Reports of the association of cadmium exposure with mutagenesis or carcinogenesis in humans and animals have generated concern. Most of the reports of mutagenicity are based on either *in vitro* techniques or *in vivo* animal experiments and are difficult to extrapolate to human exposure conditions.

4.2.5.1. Mutagenesis

When cadmium chloride was added to an *in vitro* DNA synthesis system statistically significant increases in mispaired nucleotides were demonstrated (Sirover, 1976). Takahashi (1972) induced abnormal mitotic and meiotic recombinations in the yeast, Sacharomyces cerevisiae, upon exposure to cadmium chloride. Mutant recombinants were produced in strains of Bacillus subtilis by cadmium chloride but not by cadmium nitrate (Nishioka, 1975). Costa et al. (1976) demonstrated unscheduled DNA synthesis in Chinese hamster embryo cells following exposure to cadmium chloride and cadmium acetate. Chromosomal alterations in human leukocytes were induced by cadmium sulfide (Shiraishi et al., 1972). The specific types of human chromosomal aberrations reported by Shiraishi et al. (1972) were similar to the changes observed in leukocytes from 'Itai-Itai' patients (Shiraishi and Yoshida, 1972) and in workers exposed to lead and cadmium (Deknudt and Leonard, 1975; Bauchinger et al., 1976). Mutagenic effects on genetic materials or cells from a variety of species have been demonstrated *in vitro*. When considering the *in vitro* cadmium mutagenicity data, it must be remembered that, in human or other mammalian organisms, cadmium is found bound to metallothienein and other proteins. There is little evidence for the presence of ionic cadmium in substantial amounts. The significance of *in vitro* mutagenic effects beyond their direct action for disruption of genetic processes in artificial testing systems is not clear.

Several studies appear to have shown evidence of *in vivo* mutagenic effects of cadmium at high exposure levels. This includes the demonstration of chromosomal anomalies in mouse oocytes and blocked development of metaphase I chromosomes following injection of an acute dose of 3 or 6 mg/kg of cadmium chloride (Shimada et al., 1976) and chromosomal damage in human leukocytes obtained from

'Itai-Itai' patients (Shiraishi and Yoshida, 1972) or workers exposed to cadmium and lead (Deknudt and Leonard, 1975; Bauchinger et al., 1976).

The one *in vivo* test yielding consistently negative results is that for dominant lethal mutations. In one study, for example, (Epstein et al., 1972) cadmium chloride was among 174 compounds evaluated for their ability to induce dominant lethal mutations in mice, but no significant evidence was obtained for the cadmium compounds at intraperitoneal (i.p.) doses ranging from 1.35 to 1.70 mg/kg. Nor was any evidence for such cadmium induced mutagenicity in mice obtained in a similar study by Gilliavod and Leonard (1975), using i.p. injections of 0.5, 1.75 or 3.0 mg/kg of cadmium chloride, or in a study by Suter (1975), which used cadmium chloride (2 mg/kg, i.p.).

The results of some of the above negative studies can be criticized for not being sufficiently sensitive to mutagenicity for an accurate evaluation or for lacking a sufficient number of samples. The results of Deknudt and Leonard (1975) may in part be due to lead as well as cadmium, since the human subjects in the study experienced exposure to both metals.

The studies available provide evidence for cadmium induced mutagenicity at high concentrations and especially with *in vitro* test systems. Little or no data exist for mutagenic effects occurring with oral or inhalation exposure of man or other mammalian species. The significance of *in vitro* mutagenic effects beyond their immediate implications for disruption of genetic processes in artificial testing systems therefore remains to be seen. In fact, while the mutagenic properties of some compounds may correlate with their carcinogenic potential, this does not appear to hold well in the case of cadmium or other heavy metals. The *in vitro* mutagenic effects of cadmium do not necessarily imply that the element is also carcinogenic.

4.2.5.2. Carcinogenesis

4.2.5.2 (a)

Animal Carcinogenesis Studies

There are conflicting results on the tumorigenic effects of cadmium compounds in experimental animals. Sunderman (1977) reviewed the data showing that parenteral (i.m. and s.c.) injections of cadmium powder or cadmium sulfide, oxide, sulfate, or chloride in rodents induced sarcomas at the site of injection as do a number of other substances such as glucose, iron dextrose, etc..

In addition to injection-site sarcomas, subcutaneous injection of cadmium chloride, even at a distance from the testes, often induced testicular necrosis followed by Leydig cell regeneration and hyperplasia and ultimately Leydig cell tumours (Favino et al., 1968; Gunn et al., 1963 1964, 1965, 1967; Guthrie, 1964; Haddow et al., 1964; Knorre, 1970, 1971; Lucis et al., 1972; Nazari et al., 1967; Reddy et al., 1973; Roe et al., 1964). The Leydig cell tumours produced have often been found to be functionally active in the sense of secreting large amounts of sex steroids (Gunn et al., 1973). Typically, high-level, systemic-injection doses have been employed to produce injection-site sarcomas or distal-site tumours, with the effective doses of cadmium often exceeding 1.0 mg/kg of body weight.

Leydig cell tumours observed after the parenteral (i.m. and s.c.) injection of cadmium in the above manner, however, have not yet been found to increase in incidence when cadmium is administered orally at lower dose levels (Schroeder et al., 1965; Kanisawa and Schroeder, 1969; Levy and Clack, 1975; Levy et al., 1975). Schroeder et al. (1965) and Kanisawa and Schroeder (1969) exposed rats to cadmium acetate in their drinking water (at 5 ppm) from weaning until death, up to four years later and found no significant

increase in tumours for cadmium-exposed animals in comparison to the incidence for control animals.

In the studies by Levy (1975) cadmium sulfate was administered by gastric intubation three times each week for a period of two years at doses ranging from 0-350 µg Cd/kg and to mice in the same way but once weekly for 18 months at doses ranging from 0-1.75 µg Cd/kg. No significant increase in the incidence of Leydig cell tumours was found in the cadmium-treated animals as compared with controls nor were any prostate neoplasms or pre-neoplastic changes seen in the prostate.

These results were in contrast to findings obtained following the intravenous administration of cadmium salts. The authors suggested that low gastric absorption of cadmium and a high spontaneous incidence of Leydig cell tumours in control group rats were possible reasons for the absence of a significant response in their study.

The Schroeder and the Levy studies were considered to be inconclusive, when evaluated by some working groups (IARC, 1976; Carcinogen Assessment Group, 1977). The doses employed in the Schroeder and Levy studies resulted in kidney concentrations of cadmium below those typically seen in adult humans. Some animals were sampled for possible tumour pathology and some results were stated in qualitative rather than quantitative terms making interpretation of the studies very difficult.

In a recent study from Germany (Takenaka, 1983), lung cancers were induced in male Wistar rats exposed continuously to cadmium chloride aerosols for 18 months. Among the 120 male Wistar rats the incidence of lung carcinomas reported were 71.4% in the group exposed to 50 µg CD/m^3, 52.6% in the group exposed to 25.6 µg Cd/m^3, and 15.4% in the group exposed to 12.5 µg Cd/m^3. None of the controls developed lung carcinomas.

A study by Sanders and Mahaffey (1984) investigated the carcinogenic effects of single or multiple exposures to intratracheally instilled cadmium oxide, resulting in total doses of 0, 25, 50 and 75 µg in Fischer rats. A life-table analysis detected no differences in survival among the treatment groups. Pulmonary-deposited cadmium oxide did not result in an increased number of tumours except in the mammary gland or in rats that had three or more tumour types. Cadmium oxide did not induce carcinogenic change in the lung, liver, kidney or prostate gland of the rats in this study.

Considering the positive results in a number of these studies, there is evidence that cadmium chloride, sulphate, sulphide and oxide will produce injection site sarcomas in the rat. Injection studies using cadmium chloride and cadmium sulphate have been reported to induce interstitial cell tumour of the testis in rats and mice. Oral studies of these substances have been inadequate for evaluation. The lifetime inhalation study in which rats were exposed continuously for 18 months to a cadmium chloride aerosol at low concentration showed a high incidence of primary lung cancer with evidence of a dose-response relationship (Takenaka, 1983). These results have been accepted as evidence that cadmium may have a carcinogenic potential (IARC, 1976; NIOSH, 1976; Carcinogen Assessment Group, 1978).

4.2.5.2 (b) Human Carcinogenesis Studies

The mutagenic and tumorigenic effects discussed above provide some presumptive evidence for cadmium being a carcinogen in humans. Only a relatively limited number of studies, however, have provided any relevant data on possible cadmium-induced carcinogenicity in humans. The investigations of causes of death among workers are one source of data; studies of tissue concentrations by cause of death are another source. The data are sparse and subject to the limitations of retrospective study design and autopsy studies.

The first report of a potential human cancer risk due to cadmium came from two studies in British cadmium workers. In 1965, Potts reported that eight deaths had occurred among 74 men with at least 10 years of exposure to cadmium oxide dust and that three of the deaths were from cancer of the prostate.

Potts' reports have been criticized because they did not give adequate information to relate the findings to mortality in the general population and because no data were given concerning the causes of death among exposed workers with less than ten years' exposure.

Kipling and Waterhouse (1967) reported a follow-up study of workers in the same battery plant. The search was extended to include causes of death for all those with at least one year's exposure. They found 248 workers with this exposure. Four of these workers had cancer of the prostate. (Three of these were also included in Potts' findings.) Mortality experience in an unidentified population, stated to be similar, was used to calculate the expected number of deaths for all cancers and for specific cancer sites. For the four cancer sites, and for cancers

for all sites, significant differences between observed and expected number of deaths were found only for cancer of the prostate. The expected number of deaths due to cancer of the prostate was reported to be 0.58.

Sorahan (1982) updated the study begun by Kipling and Waterhouse in 1967. The new cohort included both male and female workers with a minimum period of employment of one month who commenced employment between 1923 and 1975. The workers were classified as having "high", "slight" and "minimal" exposure to cadmium as well as by employment prior to 1947 (E) and after 1947 (L). The vital status was determined to June 30, 1980. Cause of death was taken from the death certificate. Among the males there was no statistically significant increase in deaths attributed to all cancers or for cancer of the stomach, bronchus, prostate or bladder.

A second cohort was drawn from the first cohort consisting of all males alive 15 years after first employment and having left the company by that date. This cohort was then subdivided into exposed and unexposed to cadmium, and analyzed by cause of death. The cohort was also divided into those who were employed less than one year and those who were employed from 1-14 years. There was no statistical difference between the SMR for all cancers, cancer of the stomach, bronchus, prostate or bladder between the exposed and unexposed groups, or between the groups employed less than one year or from 1-14 years. The conclusion of this paper was that their analysis did not suggest an increased risk of cancer mortality associated with exposure to cadmium oxide dust. Further analysis of a subset of the data was planned in an attempt to reconcile their negative finding relative to cancer of the prostate.

In 1983 this study was updated (Sorahan and Waterhouse, 1983). The population is essentially the same but the period of follow-up was extended to January 31, 1981. Exposure data, determination of mortality, and the external control group (the general population of England and Wales) remained the same. Analysis was by Standard Mortality Ratio (SMR) as in the 1982 Sorahan study, but also by the method of regression models in life tables (RMLT). In the SMR analysis the authors included in cancer of the respiratory system the causes of death according to the International Classification of Diseases (I.C.D.) 160-163. The 1982 study only used I.C.D. causes 162-163. Practically speaking this includes malignant neoplasms of nasal cavity, middle ear and accessory sinuses (160), the larynx (161), the trachea, bronchus and lung (162) and the pleura (163). No reason for this change is given. The 1983 paper also includes the female workers in some of the calculations but not in all of them. In the 1982 paper the female workers were not considered in the same way.

Despite the changes in the handling of the data and the small extension of follow-up time this analysis has not provided convincing new evidence that cadmium oxide is potentially carcinogenic in humans.

Holden (1980) examined the mortality of a group of 347 men who were exposed to cadmium for at least 12 months in two factories in the United Kingdom where cadmium alloys were manufactured; a second group of 624 men who worked in the second factory but at a distance of over 100 m from the cadmium workers, referred to as "Vicinity Workers", and a third "Control Group" of 537 men who worked in an iron and brass foundry.

The mortality status of the workers was determined as of December 31, 1979. The cause of death was taken from death

certificates and compared with death rates from England and Wales in 5-year groupings. This study did not find a statistically significant increase in the number of expected deaths due to cancer of the digestive, respiratory or genito-urinary systems (including the prostate), among the cadmium workers. There was an increased incidence of cancer of the prostate among those workers classed as "Vicinity Workers". These workers were exposed to other known carcinogens and exposed to less or no cadmium, therefore, this is a negative finding with respect to a relationship between cadmium and cancer.

Lemen (1976) conducted a study of occupationally-exposed workers at a cadmium smelter in the United States. This study used employment histories to establish a population of 292 workers with more than two years' exposure employed during a 30-year period between January 1940 and December 1969. It was established that by 1974, 92 had died, 180 were known to be alive, and 20 were lost to the study. Causes of death were established and standardized mortality ratios (SMR) were calculated. Mortality from cancer at all sites was found to exceed the expected mortality by a statisticaly significant margin. Among the deaths from cancer, 12 were from sites in the respiratory system. This was a significant excess, with an SMR of 235. Cancer of the prostate was found to have the highest SMR (SMR = 345, $p \sim 0.05$) 1.15 cases expected, 4 cases observed). The latency period for prostatic cancer deaths found both by Potts (1965) and Kipling and Waterhouse (1967) is 20 years or more. Lemen (1976) found the same latency period but included all deaths in the I.C.D. classification 160-164 as respiratory cancer. Histologic data for only 8 of the reported respiratory cancers was provided. The other four carcinomas could have been secondary carcinomas or malignant neoplasms of the mediastinum. It is possible that this study only showed 8 respiratory cancers with the expected

being 5.1. These results would not provide a statistically significant elevation of the incidence of respiratory cancer. This study had no smoking histories.

A mortality study among rubber workers carried out by McMichael et al. (1976) reported an SMR of 119 for cancer of the prostate, which is only slightly elevated. However, these workers were exposed to other hazardous substances as well as cadmium, and it is not possible to implicate cadmium specifically for the reported elevated level of cancer of the prostate.

In a Swedish study of 269 workers in a cadmium-nickel battery factory and 94 cadmium-copper alloy factory workers, (Kjellstrom, 1979) the risk-ratio for prostatic cancer was calculated to be 2.4, but this was not statistically significant. This study included all workers with more than 5 years' exposure to cadmium at any time since the factories started operation and included an internal reference group of 328 alloy factory workers without cadmium exposure. The authors of this paper stated that it was a preliminary report, and that they had had some problems in the collection of data on cases of cancers occurring in the 1950's.

This study was updated in 1984 (Anderson et al. 1984). The cohort consisted of male workers who had been employed in a nickel-cadmium battery factory in Sweden for more than one year, between the years 1940 and 1980. Of the 545 men identified, 17 had emigrated and 3 could not be traced. The final cohort was 525 male workers. Between 1951 and 1980, 105 men died before the age of 80. These workers were exposed to both cadmium and nickel. The cadmium levels were believed to be close to or in excess of 1 mg/m^3 until 1977 and lower after 1977. No estimate of individual dose was made, only of the period of time exposed. There was a non-

significant increase in mortality due to cancer of the prostate, 3 observed, 1.6 expected. There was a small difference in the number of deaths due to lung cancer, 3 observed, 2.5 expected, but no statistically significant increase. In those with more than 15 years exposure there was a statistically significant increased mortality due to chronic non-malignant kidney disease. This paper and the 1979 study of the same cohort did not show an increase in mortality due to cancer of the prostate or lung or any other area.

A study of the mortality of British cadmium workers was published by Armstrong and Kazantzis in 1983. They studied the mortality of a cohort of 6995 men born before 1940 and exposed to cadmium for more than one year between 1942 and 1970. They did not find an excess of deaths due to prostatic cancer. There were marginally more deaths from lung cancer than expected, but this excess was not related to exposure levels. These researchers did not have smoking histories for the cohort.

Autopsy studies have compared cadmium concentrations in tissues by causes of death. Lewis (1972) found in their series of 172 autopsies that higher concentrations of cadmium in kidney cortex, liver and lungs were found in cases of death from cancer of the bronchus and lung. However, when cigarette smoking is controlled for, these differences disappear. This forces reconsideration of the findings reported earlier by Morgan (1970, 1971), who found significantly higher cadmium tissue content for causes of death from cancer of the lung but did not control for smoking status. Voors (1975) reported on an autopsy series that they found no association between higher cadmium tissue concentrations and deaths from cancer. Kolonel (1976) reported on a survey of patients at Roswell Park Memorial Institute for an 8-year period, 1957 to 1964. All white

males aged 50 to 79 years with a diagnosis of renal cancer were compared to two control groups: one of all comparable males with non-malignant diagnoses and the second of males with cancer of the colon. From the smoking and employment histories all subjects were categorized as "exposed" or "not exposed" to cadmium via the respiratory route. Data from the dietary history were used to categorize the men as nutritionally "exposed" or not. Two sources of respiratory exposure and the dietary exposure were therefore considered. The relative risk for cancer of the kidney was increased only when smoking and occupation were considered together, in which case the age-specific, relative risk was 4.4, whereas for smoking alone, the relative risk was 1.2.

Prostatic cancer has been reported in several studies to be associated with occupational exposure to mixtures of airborne particulate matter which contained cadmium oxide as a common component. Although the evidence is not conclusive, the possibility that cadmium can cause cancer cannot be dismissed.

A comprehensive review of the carcinogenicity of cadmium with special reference to cancer of the prostate was published by Piscator in 1981. He is of the opinion that latent cancer of the prostate is very common. A number of factors such as occupation, race, sex life, socio-economic status and nutrition have been cited in studies as having influenced the incidence of cancer of the prostate. A close analysis of all reported cases of death from prostatic cancer among cadmium exposed workers showed heavy exposure to cadmium at some time in their lives. If there is a cancer-promoting action from large doses of cadmium, it is probably indirect, mediated through the hormonal systems regulating the metabolism of prostatic cells. It is also conceivable that both high prostatic cadmium concentration

and a disturbed zinc metabolism might have contributed to this effect. The controversial and contradictory evidence of a relationship between heavy exposure to cadmium and carcinogenicity, reported in the earlier literature, has not been supported by the results reported in more recent studies (Holden, 1980; Sorahan, 1982; Armstrong, 1983). There have been no studies as yet in which exposure to cadmium at levels presently expected in industry (50 - 100 $\mu g/m^3$) have been associated with an increased incidence of cancer at any site.

There is evidence in the literature which suggests that cadmium may be a factor in the etiology of human cancers at various sites, but the association has not been firmly established.

4.2.6. Reproductive Effects

There are no reports of teratogenic effects in cadmium-exposed humans. In a study of women industrially exposed to cadmium in the U.S.S.R., no malformations were detected in newborns but birth weights were lower than in newborns of controls (Smith, 1976). Some of the studies (Kuhnert, 1982; Lauwerys, 1978) in pregnant women suggest that the placenta may act as a partial barrier in low-level cadmium exposure. The placenta can accumulate cadmium. At high levels of exposure there may be toxic effects in the fetus. However, there are no studies following heavy exposure to cadmium in industry to support this theoretical conclusion. (For further detail see Section 3.2.)

4.2.7. Other Effects

Other effects reported in man after chronic industrial exposure to cadmium include mild anemia, ulceration of the nasal mucosa, anosmia and certain laboratory signs of liver damage (Friberg, 1974).

5. EXPOSURE-EFFECT RELATIONSHIPS

As discussed in the previous sections, cadmium has a long biological half-time (greater than 10 years) in humans and can cause irreversible toxic effects on the kidney. There are neither preventive methods to control the movement of cadmium to the kidney, nor any recognized mode of treatment to remove cadmium from the kidney or other soft tissues. In low level chronic exposure, there is also a long induction period between the onset of exposure and the appearance of the toxic effects of cadmium. The most effective approach in protecting workers against cadmium toxicity is to minimize or eliminate exposure to cadmium compounds.

In chronic exposure to cadmium renal damage usually precedes pulmonary impairment and on this basis the kidney is generally accepted as the critical organ. Cadmium is cumulative and the damage observed in the kidney is believed to result from the excessive accumulation of cadmium in the renal cortex following environmental and/or occupational exposure.

To help define the levels of cadmium exposure which can cause adverse health effects, it is important to review the epidemiological studies directly related to cadmium exposure in industrial workers. Some of these studies were discussed in the section on Toxicology (4.2) and will be briefly described in this section.

In a study carried out by Kjellstrom in 1974 among a group of 185 persons continuously exposed to cadmium dust in the work environment, the prevalence of increased urinary β_2-microglobulin excretion increased with employment time. For workers exposed to about 50 µg Cd/m^3 for 6-12 years the prevalence was 19% as compared with 3% in the reference (control) population (Kjellstrom, 1977).

Results from a study by Lauwerys in 1972 demonstrated excessive proteinuria in 15% of 27 workers still at work and exposed for less than 20 years to an average total cadmium dust concentration of 134 $\mu g/m^3$ and in 70% of 22 workers still at work but exposed to an average total cadmium dust concentration of 66 $\mu g/m^3$ for over 20 years.*

Although some of the reports suggest differences in the renal effects of exposure to various cadmium compounds (cadmium fumes or dust), they are minor when the respirable particle size is considered. Most of the workers who have been exposed to 50 $\mu g\ Cd/m^3$ for more than 10 years showed a significantly increased incidence of proteinuria. It has been pointed out in some of the epidemiological studies (Kjellstrom, 1977) that this estimation is very approximate because of the differences in both detection methods of proteinuria and determination of the exposure levels in the studies. Moreover, the differences in respiratory absorption rate, smoking habits of the workers, hygiene and the influence of other contaminants at the workplace should also be considered in comparing the results from different research groups.

A number of studies have been carried out in an attempt to define the early biological signs which would indicate excessive accumulation of cadmium in the kidney and to evaluate the level of internal exposure which leads to such damage. Extensive investigations were carried out by Bernard, in an attempt to characterize cadmium-induced proteinuria in workers (Bernard, 1976, 1978, 1979; Roels, 1978). Their results indicate that the nephrotoxicity of cadmium consists of a tubular and a glomerular dysfunction. Both changes can appear independently or may

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*In this study proteinuria greater than 250 mg/g creatinine in urine was considered to be excessive.

be associated, but there is no indication that one type of disturbance consistently precedes the other.

Another important objective was to attempt to determine the level of internal exposure which would induce these changes. A large study was carried out which involved 309 workers in two large cadmium smelters in Belgium (Roels, 1979). This study involved the determination of the cadmium level in both liver and kidney in each worker as well as the evaluation of their renal status by the determination of their urinary concentration of β_2-microglobulin and albumin. As a result of this study, it was concluded that following excessive exposure to cadmium, renal cortical cadmium content reaches a maximum and then rises no further. Following the development of kidney damage renal cortical cadmium decreases progressively. The critical level of cadmium in renal cortex is believed to be in the range of the highest concentration found in those workers without kidney damage (in this study, between 200 and 250 µg/g kidney cortex).

A recent study was carried out by this group using a similar protocol but also measuring cadmium in blood, and urine and determining the depth of the left kidney by echography (Roels, 1983). This allows more accurate determination of the location of the kidney cortex and therefore more accurate determination of the cadmium content of the kidney cortex. As a result of the 1983 study, it was concluded that a value of 216 ppm (µg/g) of cadmium in kidney cortex was the best estimate of the critical level for groups of male workers exposed to cadmium and that this value would be associated with a urine cadmium level of 10.8 µg/g creatinine.

The critical concentration of cadmium in the kidney has been calculated in a number of studies on cadmium workers as well as those exposed to cadmium environmentally. These data are

summarized in Table 4 and are based on estimation of cadmium in the kidney either from autopsy or biopsy samples from exposed people, or from an *in vivo* measurement by neutron activation techniques. Since these values are based on a few measurements, the exact magnitude of the critical renal concentration of cadmium is still controversial. However, the general conclusion from recent work is that cadmium levels in the kidney cortex below 200 µg/g are safe in at least 90% of cases. This level is, at present, therefore regarded as the "threshold" for a critical effect. There are marked variations in the reported values of cadmium in the renal cortex in workers with renal disease and some of these values are even lower than the renal cadmium concentrations in those without renal damage. These differences can be partly explained by the increased urinary excretion of accumulated cadmium from the kidney in workers following the development of renal damage.

6. RELATIONSHIP BETWEEN EXPOSURE TO CADMIUM AND CADMIUM CONTENT OF KIDNEY CORTEX

6.1 Description of Model

One mathematical model is available to make estimates of the concentration of cadmium in the kidney cortex for various types of exposure to cadmium. The model uses several parameters, the values of which are not precisely known. The model consists of two parts: one part describes the absorption of cadmium from air into blood via the lung and gastro-intestinal tract (GI tract) (Task Group on Lung Dynamics, 1966), and the other part of the model describes the accumulation in the kidney cortex of cadmium absorbed from blood (Friberg et al.,1974).

The first part of the model describes the deposition of the particles of cadmium which are inhaled into the lung (Task Group on Lung Dynamics, 1966). This model of the

respiratory system was developed for a wide variety of dust particles and for application to radioactive particles and is applied to cadmium specifically in these calculations. According to this model, the respiratory system is divided into three parts called the naso-pharyngeal region (NP Region), the tracheo-broncheal region (TB Region) and the pulmonary region (P Region). The fraction of the inhaled particles deposited in each of these three regions depends upon aerodynamic diameter of the particles and tidal volume.

The aerodynamic diameter of a particle is defined in terms of the terminal velocity in air of unit density spheres. Two particles have the same aerodynamic diameter when the terminal velocities in air are the same. Terminal velocity depends upon diameter, density and geometry. Tidal volume is the volume of gas inspired or expired during each respiratory cycle (Comroe, 1965).

Dust particles in air normally have a range of sizes and the frequencies of the various sizes have been shown to be well-described by a log-normal curve. The mass median aerodynamic diameter is an important factor which determines the amount of dust deposited in each lung compartment.

Table 6 shows the fraction of inhaled particles which are deposited in each part of the respiratory system according to the aerodynamic size of the particle and the tidal volume. A tidal volume of 750 cm^3 is representative of a mild to moderate activity state (Task Group on Lung Dynamics, 1966). The table shows that for aerodynamic diameter less than 1μ, the fraction of particles deposited in the NP region is 0 and increases to almost 100% as the aerodynamic diameter increases to 10 μ. Deposition in the TB region is about 30% for particles which have an aerodynamic diameter of 0.01 μ to 0.02 μ, decreases to about 2%-6% between 0.02 μ and 1 μ, increases to 5-9% between 2 μ and 6 μ and decreases to 1% for larger particles.

Deposition in the P region is between 50 and 60% for particles between 0.01 μ and 0.06 μ. It varies between 20 and 35% between 0.02 μ and 4.0 μ and decreases to less than 10% for particles greater than 6 μ.

The clearance from the lung of deposited particles is also described. Figure 1 shows a schematic representation of the three parts of the respiratory system. The deposited substance is transferred from the lung to the blood, GI tract and the lymphatic system. The kinetics of the transfer are described in terms of single exponential functions and regional fractions. The parameters of clearance depend on the compound class. Class D compounds are cleared from each compartment within a few days. Large amounts of these compounds are removed from the TB region and the P region by absorption into the blood. The amount absorbed into blood from the NP region is equal to the amount translocated to the GI tract. Class W compounds are cleared from the NP region and TB region in a day or two and clearance from the P region takes several weeks. For these compounds, about 90% of the material deposited in the NP region is translocated to the GI tract and equal parts are translocated from the TB region to the GI tract and to blood. About 20% of the material deposited in the P region is translocated to blood or the lymph nodes and the remainder is removed to the GI tract. For the Class Y compounds, removal from the NP region and the TB region occurs in a day or two while clearance from the P region occurs with a half-time of 500 days for most clearance pathways. In this model, 99% of the material deposited in the NP region and the TB region is translocated to the GI tract and about 80% of the material deposited in the P region is translocated to the GI tract.

The clearance kinetics for cadmium compounds are not known and it may be that different compounds of cadmium are cleared at different rates from the respiratory system. In

particular, the amounts of material deposited in a compartment which are subsequently translocated to blood and to the GI tract are not known for cadmium compounds. The Task Group on Lung Dynamics, however, classifies all cadmium sulfates, carbonates and phosphates as class D compounds, all cadmium carbides, sulfides, halides and nitrates as class W compounds and all cadmium oxides and hydroxides as class Y compounds.

As noted before, the size of dust particles in the air varies and the size of the dust particles determines the amount deposited in the respiratory tract. Because the variability in the sizes of dust particles will likely depend upon the type of work being done, calculations of the amount of cadmium deposited will be done for a variety of particle sizes. The results of these calculations can be used to estimate the amount deposited as a result of breathing air containing dust of a particular size distribution.

As an example of the application of the first part of the model, the average amount of cadmium absorbed per day for a worker exposed to air containing cadmium particles at a concentration of 20 $\mu g/m^3$ and each particle having an aerodynamic diameter of 4 μ is calculated. The volume of air inspired by a worker involved in light to moderate activity for eight hours is taken to be 10 m^3.

The fraction of inhaled cadmium deposited in the NP region is 0.654 and the mass of cadmium deposited in the NP region during the work day is calculated to be

$$10\ m^3 \times 20\ \mu g/m^3 \times 0.654 = 130.8\ \mu g$$

The fraction of inhaled cadmium deposited in the TB region is 0.084 and the mass of cadmium deposited in the TB region during the work day is calculated to be

$$10\ m^3 \times 20\ \mu g/m^3 \times 0.084 = 16.8\ \mu g$$

The fraction of inhaled cadmium deposited in the P region is 0.238 and the mass of cadmium deposited in the P region during the work day is calculated to be

$$10\ m^3 \times 20\ \mu g/m^3 \times 0.238 = 47.6\ \mu g$$

In order to calculate the average amount of cadmium deposited per day, each of these values should be corrected for vacation days and the five-day work week. Of the 365 days in the year, 250 are assumed to be spent exposed to cadmium even though the average value is likely between 230 and 240 days. Consequently, the average mass of cadmium deposited per day in the NP region, TB region and the P region is respectively:

$$130.8\ \mu g \times 250/365 = 89.6\ \mu g$$
$$16.8\ \mu g \times 250/365 = 11.5\ \mu g$$
$$47.6\ \mu g \times 250/365 = 32.6\ \mu g$$

According to the clearance model for Class Y compounds, 1% of the mass deposited in the NP region region is translocated to the blood and the remainder is moved to the GI tract where about 5% is absorbed into blood.

Hence, the total mass of cadmium absorbed into blood directly or indirectly from the NP region is calculated to be

$$89.6\ \mu g \times 0.01 + 89.6\ \mu g \times 0.99 \times 0.05 = 5.3\ \mu g/day$$

The fraction of cadmium translocated from the TB region to blood is 0.01 and the fraction translocated to the GI tract is 0.99.

The total mass of cadmium absorbed into blood directly or indirectly from the cadmium deposited in the TB region is

$$11.5\ \mu g \times 0.01 + 11.5\ \mu g \times 0.99 \times 0.05 = 0.7\ \mu g/day$$

The fraction of cadmium translocated from the P region to the blood is 0.05. The fraction translocated from the P

region to the lymph nodes is 0.15 and the fraction translocated from the lymph nodes to blood is 0.9. The fraction of cadmium translocated to the GI tract with a half-time of 1 day is 0.4 and with a half-time of 500 days is 0.4.

Hence, the total amount absorbed into blood from the P region is

$$32.6\ \mu g \times 0.05 + 32.6\ \mu g \times 0.4 \times 0.05 + 32.6\ \mu g \times 0.4 \times 0.05 + 32.6 \times 0.15 \times 0.9 = 7.3\ \mu g/day$$

Hence, the total amount of cadmium absorbed into blood from the lung is

$$5.3\ \mu g + 0.7\ \mu g + 7.3\ \mu g = 13.3\ \mu g/day$$

This value represents the average daily amount of cadmium absorbed when the time from the start of cadmium exposure is large. The clearance model gives the kinetics of the transfer of cadmium from each part of the respiratory system to the blood and the GI tract. Clearance from the NP region and the TB region occurs in a few hours according to the model while clearance from the P region and the lymph nodes occurs over several years. Immediately after the start of exposure little of the cadmium deposited in the P region is removed. As the amount of cadmium in the P region builds up, the mass of cadmium which is removed increases until the amount cleared per day is the same as the amount deposited per day. The model indicates that this equilibrium condition is reached in the lung after about eight years of exposure if cadmium is cleared according to the class Y model.

It is of interest to note that the amount of cadmium absorbed into blood for large aerodynamic diameters is similar to the amount absorbed for small aerodynamic diameters. In particular, for a particle which has an aerodynamic diameter of 10 μ, the average amount of cadmium

absorbed into blood per day is 8.21 μg when the cadmium dust concentration is 20 $\mu g/m^3$. The calculation of this quantity is shown below.

Average amount of cadmium deposited in NP region is calculated to be

$$10\ m^3/day \times 20\ \mu g/m^3 \times 0.992 \times 250/365 = 135.9\ \mu g/day$$

Average amount of cadmium deposited in the TB region is calculated to be

$$10\ m^3/day \times 20\ \mu g/m^3 \times 0.007 \times 250/365 = 0.96\ \mu g/day$$

Average amount of cadmium deposited in P region is calculated to be

$$10\ m^3/day \times 20\ \mu g/m^3 \times 0.002 \times 250/365 = 0.27\ \mu g/day$$

Average amount of cadmium absorbed per day into blood from NP region is calculated to be

$$135.9\ \mu g/day \times 0.01 + 135.9\ \mu g/day \times 0.99 \times 0.05 = 8.09\ \mu g/day$$

Average amount of cadmium absorbed per day into blood from the TB region is calculated to be

$$0.96\ \mu g/day \times 0.01 + 0.96\ \mu g/day \times 0.99 \times 0.05 = 0.06\ \mu g/day$$

Average amount of cadmium absorbed per day into blood from the P region is calculated to be

$$0.27\ \mu g/day \times 0.05 + 0.27\ \mu g/day \times 0.4 \times 0.05 + 0.27\ \mu g/day \times 0.4 \times 0.05 + 0.27\ \mu g/day \times 0.15 \times 0.9 = 0.06\ \mu g/day$$

The total amount absorbed per day at equilibrium is

$$8.09 + 0.06 + 0.06 = 8.21\ \mu g/day.$$

Another part of the model describes the amount of cadmium in the kidney cortex as a function of time (Friberg et al.,

1974). In this part of the model, it is assumed that, at any time, one-third of the body burden of cadmium is located in the kidney and the concentration in the kidney cortex is 50% greater than the mean concentration in the kidney. The kidney's mass is assumed to be 300 g. It is also assumed that the accumulation of cadmium in the kidney cortex under conditions of constant exposure is described by the function

$$B(t) = \left(\frac{1}{3} \times \frac{1.5}{300}\right) \frac{a}{f} (1 - e^{-ft})$$

where $B(t)$ = the concentration of cadmium in the kidney cortex at age t

a = uptake of cadmium per unit time

f = fraction of body burden of cadmium excreted per unit time

The parameter f is related to the biological half-time.

$$f = \ln 2 / T_{1/2}$$

where $\ln 2$ = natural logarithm of 2 (0.693)

$T_{1/2}$ = biological half-time of cadmium in the body.

The other major sources of cadmium exposure are food and cigarette smoke. As noted previously, a 20 cigarette per day smoker inhales between 2 and 4 µg of cadmium per day and about 50% of these fumes are deposited in the lung and about 50% of the deposited cadmium fumes are absorbed into the blood. Hence, about 25% of the cadmium inhaled in cigarette smoke is absorbed into the blood from the cigarette smoke inhaled into the lung. Smoking 20 cigarettes per day results in the absorption of between 0.5 and 1 µg of cadmium per day into the lung. In the model, it is assumed that cigarette smoking begins at age 20.

Most of the uptake of cadmium for non-occupationally exposed persons is from food. As noted previously, the dietary intake of Americans is estimated to be 40 µg per day while the dietary intake of Canadians is estimated to be between 60 and 80 µg per day. The average adult Canadian diet was assumed to contain 2800 calories per day on the basis of the caloric intake of Swedish males. Based on these data, the cadmium content of the Canadian diet is between (60 µg/day)

(2800 calories/day) = 0.02 µg/cal and 80 (µg/day) (2800 cal/day) = 0.03 µg/cal. The caloric content of the diet of Swedish males increases from birth and reaches a peak at about age 18. It declines quickly between 18 and 20 years of age and declines slowly after 20 years of age. This assumed relationship between age and daily caloric intake of the diet understates the relationship between age and daily caloric intake (Health and Welfare Canada, 1976). The average Canadian diet of males contains 3375 calories/day between age 20 and 39, and 2675 calories/day between 40 and 64. The cadmium content of the diet was assumed to be 0.02 µg cadmium/calorie for all ages.

The biological half-time, as discussed previously, is not precisely known and the estimates for the value are between 10 years and 33 years. As shown above, the larger the value of $T_{1/2}$ the smaller the amount of cadmium excreted per day and as a result, a larger half-time results in larger accumulation of cadmium in the body and, in particular, in the kidney cortex. Because of the uncertainty in the value of the biological half-time and because this parameter has an important influence on the results of the model calculations, separate calculations were performed using three values for $T_{1/2}$ namely, 10, 21.5 and 33 years.

Another mathematical model which uses eight compartments to model the absorption and distribution of cadmium in the body (Kjellstrom et al., 1978) is available. The model consists of several single exponential functions which describe the flow of cadmium between various compartments in the body. The respiratory characteristics described by the Task Group on Lung Dynamics (Task Group on Lung Dynamics, 1966) were used to model the absorption of cadmium. After absorption from the lung or the GI tract, cadmium is transferred to and from the liver, kidneys, other tissues and various components of blood. Eventually, excretion in urine or faeces occurs. A schematic description of the model is shown

in Figure 2 and the equations and constants used are shown in Figures 3 and 4. Kjellstrom et al. used data in occupationally-exposed men and occupationally-unexposed men to evaluate the parameters of the model.

The model also contains two parameters which are age-dependent. According to the model, excretion of cadmium from the kidney increases continuously after the age of 30 and transfer of cadmium from blood to kidney decreases continuously from age 30 years. This model was used to estimate the effects of exposure to cadmium in the workplace for either 30 or 45 years beginning at age 20. This involved evaluating the maximum of the function K(t), (see figure 3) as t was increased from 0 to 80 years. Smoking was assumed to begin when t achieved the value of 20 years and it was assumed that 20 cigarettes per day were smoked. As can be seen from figure 3, the model involves calculating the amount of cadmium in each compartment at various times which are 1 time unit apart. In these calculations the time unit was 1 day. The concentration of cadmium in the kidney cortex was estimated using this model for 3 concentrations of cadmium in the workplace.

6.2 Limitations of Models

The use of first order exponential models is valid when the model is applied to situations where the differences in concentrations in two compartments regulate completely the flow of the substance. In particular, the rate of transfer of cadmium from one compartment to another is proportional to the difference in concentration in the two compartments. It has been pointed out that absorption of cadmium in the tubules of the kidney occurs against a concentration gradient and for that reason, the single exponential model may be inappropriate. In these model calculations it is asumed that no kidney damage results from the exposure to cadmium and thus the calculated values will

be inappropriate at high levels of exposure following the onset of kidney damage.

This model should link the exposure of a population of workers to the proportion of workers who will suffer kidney damage from that exposure. Kidney damage may not be a simple function of the concentration of cadmium in the kidney cortex (Nordberg et al., 1982). It may well be that the risk of damage depends upon the time course of exposure. The critical value of 200 µg/g has been derived from rather high rates of exposure (i.e., high concentrations in the workplace) and it has been speculated that lower rates of exposure may produce more than proportionately lower levels of risks.

A preliminary calculation attributed to Holmberg et al. has shown the risk of proteinuria as a function of daily intake of cadmium for 2 values of the fraction absorbed from the GI tract (Nordberg et al., 1982). These curves indicate that the risk of proteinuria increases smoothly as a function of intake and that there is no absolute threshold level of exposure for risk and that the risk from a given exposure may depend upon other health conditions such as anaemia.

6.3 Results of Model Calculations

The results of the model calculations based on the single exponential function are shown in Table 7 for smokers and non-smokers who are not exposed to cadmium at the workplace.

Tables 8a, 8b and 8c show the results of calculations based on the single exponential function for the class Y, W and D lung clearance models for smokers who are exposed to 1, 20 or 50 µg Cd/m^3 for either 30 years or 45 years in the workplace using different estimates (10, 21.5 or 33 years) of the biological half-time of cadmium in the body and various aerodynamic diameters.

Table 9 shows the results of the calculations based on the 8 compartment model for smokers and non-smokers who are not exposed to cadmium in the workplace and for smokers and non-smokers who are exposed to 1, 20 or 50 μg Cd/m^3 for either 30 or 45 years.

6.4 Discussion

The single exponential model gives a variety of results depending upon the value of the biological half-time. The longest biological half-time used is 33 years and comparison of the calculated results with the observed data shown in Table 2 appears to indicate that the results based on a 33-year biological half-time overstate the concentration of cadmium in the kidney cortex for non-occupationally exposed persons. Although no data concerning the cadmium content of the kidney cortex in Canadians who are not occupationally exposed are available, the value of 10 years for the biological half-time results in calculated values which are comparable to the cadmium concentrations in the kidney cortex observed in unexposed Americans.

The eight compartment model produces results for non-occupationally exposed individuals which are comparable to those observed in the kidney cortex for Americans and are similar to the values calculated using the smaller values of the biological half-time in the single exponential model. The eight compartment model is an improvement over the single exponential model. The results from the single exponential model, however, are useful in assessing the relative effects of various particle sizes and chemical characteristics upon the concentration of cadmium in the kidney cortex.

The single exponential model was applied to occupational exposures using three types of lung clearance model. When the Class D model was used, an exposure level of 20 $\mu g/m^3$ or

higher resulted in calculated values which exceeded the critical level, while, according to this model, an exposure level of 1 $\mu g/m^3$ did not produce values greater than the critical value. The Class W lung clearance model produced calculated values which exceeded the critical value for some particle sizes when the exposure level was 20 $\mu g/m^3$ or greater, and exposure to 1 $\mu g/m^3$ produced calculated values which were well below the critical value. The Class Y lung clearance model produced calculated results which were below the critical value when the exposure level was below 20 $\mu g/m^3$, and the 10 year biological half-time was used. The critical value was exceeded for exposures of 20 $\mu g/m^3$ when the biological half-time was 21.5 years and the particle size was 0.06 microns or less. For other particle sizes and a 21.5 year biological half-time, the calculated results did not exceed the critical value.

The results calculated on the basis of the eight compartment model indicate that exposure levels below 20 $\mu g/m^3$ do not result in critical concentrations of cadmium in the kidney cortex.

It appears that based on the results of the model calculations, an exposure level of 50 $\mu g/m^3$ would result in critical concentrations in the kidney cortex under most conditions of exposure.

7. SUMMARY AND CONCLUSIONS

The predominant effects of low-level chronic exposure to cadmium in workers are renal and pulmonary damage. The relative severity of renal versus pulmonary damage is dependent on the intensity of the exposure (and presumably also on variations in individual susceptibility). With more intense exposure relatively more lung damage is seen, whereas with low exposures for very long time periods isolated renal damage is more likely to develop.

The carcinogenicity of cadmium was discussed in section 4.2.5.2. The experimental work in animals would appear to provide sufficient evidence for the carcinogenicity of cadmium and certain cadmium compounds in experimental animals. The available human epidemiologic data is limited and inconsistent. The data for human carcinogenicity at this time is inadequate.

As the kidney is the critical organ in long-term, low-level exposure to cadmium it is important to estimate the threshold exposure level below which, in most people, there will be no kidney dysfunction. Renal dysfunction, for this purpose, has been characterized as increased total proteinuria, or increased excretion of β_2-microglobulin and/or increased urinary cadmium excretion resulting from tubular dysfunction and/or glomerular dysfunction.

Although a number of indicators of renal dysfunction are used for the evaluation of cadmium toxicity, none of these can be considered as specific indicators of cadmium exposure, with the exception of blood and urinary cadmium. In workers with long-term exposure to relatively low concentrations of cadmium, urinary cadmium excretion did not usually exceed 10 µg/g creatinine in those with normal kidney function whereas workers with renal dysfunction excreted considerably larger amounts of cadmium. Thus, the determination of urinary cadmium can be considered as a useful tool to monitor long-term low-level exposure to cadmium. The available evidence leads to the conclusion that if urinary cadmium levels do not exceed 10 µg Cd/g creatinine, kidney dysfunction should be prevented. Monitoring of urinary concentrations of cadmium does not, however, provide accurate data on recent exposure to cadmium.

The measurement of blood cadmium levels is also a useful indicator of exposure. In persons with long-term exposure,

blood cadmium reflects approximately the exposure of the previous two to three months.

Information has been presented in this document which demonstrates the association between exposure to airborne cadmium compounds, the concentration of cadmium in the kidney and the risk of kidney dysfunction.

A number of studies of kidney function and cadmium content of renal cortex have been carried out and the best estimate of the critical cadmium content of renal cortex is approximately 200 ppm (µg/gm). At this level of cadmium in renal cortex, urinary cadmium excretion rarely exceeds 10 µg/g creatinine.

There is epidemiological evidence which demonstrates that 10-20 years of occupational exposure to an average value of total cadmium dust of 0.05 mg/m^3 will produce a significant increase in the incidence of signs of renal dysfunction among some exposed workers.

Section 6 of this document demonstrated the relationship between various exposure levels and the calculated concentrations of cadmium in the kidney cortex. Careful evaluation of these calculations supports the conclusion drawn from the clinical and epidemiological studies that occupational exposure to 0.05 mg/m^3 of total cadmium dust will produce a significant increase in the concentration of cadmium in the kidney cortex beyond what is believed to be the critical level but exposure to less than 20 $\mu g/m^3$ should not.

8. RECOMMENDATION

It is recommended that in the Province of Ontario the time-weighted average exposure limit for total cadmium dust and fume should not exceed 0.02 milligrams of cadmium per cubic metre of air with the exception of cadmium seleno sulphide and cadmium seleno-sulphide pigments. The time-weighted average exposure limit for these cadmium pigments should not exceed 0.05 milligrams of cadmium per cubic metre of air (see addendum)

It is also recommended that a maximum exposure level for a time period of less than one hour to cadmium oxide fume and total cadmium dust be established at a concentration of 0.25 milligrams of cadmium per cubic metre of air provided the above time-weighted exposure is respected.

ADDENDUM

Cadmium Pigments

Exposure in the cadmium pigment industry can be thought of in two reasonably distinct sectors 1) the production of cadmium pigments and 2) the secondary use of manufactured cadmium pigments, as colourants and stabilizers when there is no production of cadmium pigments in the same facility.

The cadmium health effects document concludes that the kidney is the critical organ. The effects on the kidney are related to the bioavailability of the compound.

The available research has been reviewed (see below) and the conclusion is that the bioavailability of cadmium pigments in production is significant and that kidney dysfunction has been identified, of the type described in the cadmium health effects document, as a result of exposure to cadmium pigments in production. The bioavailability of cadmium pigments when exposure is limited to the use of the pigments is much less. The cadmium levels measured in these workers in the studies examined were very close to the levels found in control workers who had no exposure to cadmium pigments in production or in secondary use.

Research carried out by L. W. Miksche (1981) measured cadmium in blood (CdB) and cadmium in urine (CdU) in two groups of workers; group A (A) were 36 workers employed in cadmium pigment production with a mean age of 41.5 years and a mean employment period of 11.75 years (Table I). Group B (B) were 21 workers occupied solely in the use of cadmium pigments with a mean age of 39.8 years and a mean employment period of 11.3 years. (Table 2)

TABLE 1

Cadmium concentrations in blood and urine
and
$\beta_2$microglobulin (β_2M) concentrations in urine of Group A

	Cadmium in Blood (µg/100 ml)	Cadmium in U (µg/g creatinine)	$\beta_2$microglobulin (µg/g creatinine
Mean ± $2s_m$	1.03 ± 0.24	8.78 ± 2.18	77.35 ± 22.36
Range	0.2 - 3.6	0.5 - 38	17.6 - 304

s_m = standard error of the mean

TABLE 2

Cadmium concentrations in blood and urine of workers in Group B and in controls

	Group B		Controls
	Cadmium in Blood (µg/100 ml)	Cadmium in Urine (µg/g creatinine)	Cadmium in Urine (µg/g creatinine)
Mean ± $2s_m$	0.134 ± 0.029	1.54 ± 0.29	1.26 ± 0.26
Range	0.04 - 0.30	0.4 - 3.1	0.2 - 3.0

s_m = standard error of the mean

The control levels shown in Table 2 were derived from the examination of an age-matched group of workers with similar smoking habits and no exposure to cadmium. The conclusion drawn from this examination was that exposure during cadmium pigment production produced significantly higher levels of CdB and CdU than did exposure in the use of prepared cadmium pigments. The CdU levels in Table 2 suggest that the chronic exposure to cadmium in Group B was not enough to raise the CdU levels beyond those of the control group. It would appear that the cadmium in blood levels of Group B were within the range of the non-cadmium exposed general population.

We have received from Blythe Colours Limited the results of a similar study by Dr. E. G. Hughes based on biological monitoring of workers in a cadmium pigment production plant in the United Kingdom. The work force is divided into three groups:

1. 40 men employed in cadmium pigment production- exposure to soluble cadmium compounds and finished cadmium pigment, average exposure 6.5 years (Table 3).

2. 16 men employed in cadmium pigment production- exposure to finished pigment during milling, blending and packing, average exposure 8 years (Table 4).

3. 23 men employed in master batch production - finished cadmium pigments incorporated into plastics, average exposure 9 years (Table 5).

4. 62 non-exposed persons in the control group (Table 6).

The survey examined:

Cadmium in blood (CdB)
Cadmium in urine (CdU)
β_2 microglobulin in urine (β_2U)
Cadmium in air (CdA)

TABLE 3

Average Values for Group 1

	CdB	CdU	β_2U	CdA
	µg/100 ml	µg/L	µg/L	µg/m^3
mean	0.34	4.1	103	177
range	0.10 - 0.7	<3 - 12	33-290	28-535

TABLE 4

Average Values For Group 2

	CdB	CdU	β_2U	CdA
	µg/100 ml	µg/L	µg/L	µg/m^3
mean	0.31	3.4	109	138
range	0.12 - 0.58	<3 - 4.4	25-243	36-269

TABLE 5

Average Values for Group 3

	CdB	CdU	β_2U	CdA
	µg/100 ml	µg/L	µg/L	µg/m^3
mean	0.27	3.59	108	102
range	0.07 - 0.48	<3-5.4	14-805	23-243

TABLE 6

Non-exposed or Control Group

	CdB	CdU
	µg/100 ml	µg/L
mean	0.19	<3
range	0.05 - 0.67	<3

This group was then re-examined dividing them into smokers and non-smokers and the blood cadmium (CdB) and urine cadmium (CdU) were compared (Table 7 and Table 8 respectively).

TABLE 7

Blood Cadmium µg/100 ml

	Non-smokers	Smokers
Group 1 - Mixed exposure	0.32	0.37
Group 2 - Finished pigment Milling, etc.	0.20	0.38
Group 3 - Finished pigment Masterbatch	0.22	0.33
Group 4 - Non-exposed	0.18	0.20

This was an interesting assessment and suggests that the blood cadmium of nonsmokers in group 1 (cadmium pigment production) is approximately 50% greater than the other 3 groups. This difference would appear to be masked as a result of smoking.

TABLE 8

Urinary Cadmium µg/L

	Non-Smoker	Smokers
Group 1 - Mixed exposure	3.96	4.4
Group 2 - Finished pigment Milling, etc.	3.24	3.58
Group 3 - Finished pigment Masterbatch	3.48	3.60
Group 4 - Non-exposed	<3	<3

The urine cadmium levels are similar in all three exposed groups -- the author's suggested explanation is contamination of the samples as they were collected in the factory. This study is interesting but I do not believe it has been published. Some of this information was presented at a cadmium seminar held in London, England in March of 1980. This data has also been submitted to the British Occupational Health Society (BOHS).

A biological assessment of workers employed in the secondary usage of cadmium pigments was carried out by Wibowo et al. (1982). A total of 124 workers were chosen from five different factories involved in the secondary usage of cadmium pigments. In each factory an equal number of exposed (E) and non-exposed(C) were selected by the occupational physician. Controls were matched for age, smoking habit and ethnic origin. On the same day venous blood and spot urine samples were collected. Table 9 shows the geometric mean and 67% range of CdB, CdU and β_2M levels in the exposed and control groups. Table 10 shows the results for the 34 matched pairs. In Table 9 the levels were marginally higher than control levels, the difference however, was not statistically significant with the exception of the aero-engine factory in which there was a very real possibility of cadmium oxide fume exposure. In Table 10

statistical analyses of the 34 matched pairs only established a significant difference in CdU levels. These CdU levels would not usually be considered excessive. Significant correlation between CdU and age and CdB and smoking habits was found.

The conclusion of this study was that second degree usage of cadmium pigments does not produce a significant change in CdB but only a difference in CdU indicating an increased body burden due to long term low level occupational exposure. The study reaffirmed that age and smoking habits must be taken into account when assessing exposure to cadmium.

In a study carried out by De Silva and Donnan (1981) 12 men employed in the production of cadmium pigments were examined. Increased cadmium in blood and in urine were found as well as signs of pulmonary dysfunction. This paper supports the view that the cadmium exposure associated with the production of cadmium sulfide and selenosulfide pigments is hazardous to both the kidney and the respiratory system. The paper did not address the exposure of the workers involved in the use of finished cadmium pigments.

These studies all support the conclusion that exposure to cadmium sulfide pigments, when it is not associated with production, does not increase the cadmium body burden of the exposed worker to the same extent as exposure to other inorganic cadmium compounds or exposure to cadmium in pigments during production. Cadmium pigments are considered to be non soluble cadmium compounds. Their decreased bioavailability has been attributed to this characteristic.

The evidence submitted would support a less stringent exposure level for workers whose exposure is limited to the secondary use of cadmium pigments if the critical effect is considered to be kidney damage.

TABLE 9

Geometric mean and 67% range (between brackets) of CdB, CdU and β_2M levels in exposed and control groups in each factory. Student's t-test is used to investigate possible difference between exposed and control groups (two tailed).

Factory	Groups	Cadmium in blood (µg/l)	Cadmium in urine (µg/g Creatinine)	B_2 microglobulin (µg/g Creatinine)
Glass Bottle prod. plant	E = 12	3.2 (2.4-4.3)	0.47 (0.18-1.23)	40 (24-68)
	C = 12	2.7 (1.9-3.9)	0.33 (0.14-0.75)	38 (28- 51)
Plastics prod. plant	E_1 = 9	2.9 (1.5-8.3)	0.80 (0.15-4.24)	87 (30-1335)
	E_2=12	2.8 (1.7-6.8)	0.49 (0.13-1.34)	63 (23- 93)
	C = 10	2.1 (0.6-5.5	0.39 (0.06-1.30)	83 (20- 260)
Cd plating dept. aero-engine fact.	E = 6	4.4 (2.3-13.2)[a]	1.22 (0.46-3.40)[a]	61 (30-158
	C = 8	1.7 (0.9-2.1)	0.56 (0.34-0.73)	51 (24-150
Wallpaper decor. plant	E = 18	2.7 (0.9-4.9)	0.80 (0.27-2.16)	69 (8-543)
	C = 25	3.0 (1.3-5.3)	0.63 (0.23-1.50)	83 (26-241)
T.V. tube factory	E = 6	2.4 (1.9-3.7)	0.70 (0.30-1.70)	25 (8-135)[a]
	C = 6	3.1 (2.0-4.5)	0.60 (0.30-0.90)	88 (28-184)

C = Control group; E = exposed group; E_1 = mixing dept; E_2 = rolling mill dept. Statistically different between C and E

a statistically different between C and E

TABLE 10

Matched-pair study of 34 pairs of male workers, matched according to age, smoking habits, ethnic origin and factory. The CdB+, CdU+ and β_2M +levels are expressed as geometric mean and 67% + range; the Creatinine in urine, Hb-and Ht-levels as arithmetic mean and SD. To test the difference between pairs, the paired Student's t-test has been used

	Exposed		Control	
CdB (µg/l)	2.84	(1.75-4.61)	2.67	(1.81-3.95)
CdU (µg/g Creatinine)*	0.67	(0.27-1.64)	0.48	(0.21- 1.06)
β_2M (µ/g) Creatinine)	71	(26-190)	79	(39-161)
Creatinine (g/l)	1.58 ± 0.76		1.70 ± 0.69	
Hb (mmol/l)	9.88 ± 0.55		9.93 ± 0.74	
Ht (%)	45.5 ± 2.8		46.3 ± 3.1	

*Significantly different P <0.05, two tailed

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Table 1.

Cadmium in blood (ng/ml) of control population in various countries.

COUNTRY/AREA	MALES		FEMALES	
	Smokers	Non-Smokers	Smokers	Non-Smokers
Belgium/Brussels	2.0 (29)	1.1 (57)	2.0 (15)	0.9 (40)
China/Beijing	1.8 (68)	0.6 (52)	2.6 (2)	0.8 (118)
India/Ahmedabad	1.1 (17)	0.9 (83)		0.8 (100)
Bangalore	0.7 (16)	0.7 (16)		0.9 (44)
Calcutta	0.7 (16)	0.7 (34)		0.8 (50)
Israel/Jerusalem	1.6 (37)	0.5 (96)	1.1 (17)	0.5 (51)
Mexico/Mexico City	3.9 (12)	0.3 (19)	2.1 (13)	0.4 (31)
Peru/Lima	2.9 (9)	1.0 (36)	1.2 (20)	0.8 (142)
Sweden/Stockholm	1.8 (42)	0.2 (62)	1.5 (42)	0.3 (64)
U.S.A./Baltimore	1.1 (20)	0.6 (35)	1.0 (39)	0.5 (85)
Yugoslavia/Zagreb	3.6 (27)	0.6 (33)	2.7 (45)	0.5 (87)

Data taken from a W.H.O. Monitoring study (Vahter, M. 1982).

The results are mean values and the number of samples analyzed are shown in parenthesis.

Table 2.

Mean cadmium concentration in renal cortex at about age 50.

COUNTRY	CADMIUM CONTENT (µg/g wet weight)	
	Non-Smokers	Smokers
Belgium	27.6	39.3
China	15.2	19.0
India	18.0	18.4
Israel	22.9	
JapanB (Kobe)		60.0
JapanB (Kanazawa)		85.0
JapanB (Tokyo)		125.0
U.S.A.	22.0	35.0
Yugoslavia	20.0	34.0

A Data calculated from Friberg L. et al. 1974 and Vahter, M. 1982.

B Smokers and non-smokers are not separated.

Table 3.

Biological parameters of control subjects and cadmium workers with and without renal dysfunction.

	CONTROL	CADMIUM-EXPOSED	
	Subjects	Without renal dysfunction	With renal dysfunction
A. Studies from U.S.A.			
Numbers of subjects	10	33	18
Exposure history (years)	none	0.1-34	10-34
Blood cadmium (ng/ml)	2.0	15.0	24.0
Urine cadmium (μg/ml)	2.3	9.4	22.8
Urine β_2-microglobulin (μg/g creatinine)	83.5	211.0	9161
Proteinuria (mg/g)	<250	<250	>250
B. Studies from Belgium			
Number of subjects	21		18
Exposure history (years)	none		8-40.5
Blood cadmium (ng/ml)	3.5		24.7
Urine cadmium (μg/g (creatinine)	2.4		27.5
Urine β_2-microglobulin (μg/g creatinine)	120		4080
Proteinuria (mg/g creatinine)	130		342

Data is calculated from Ellis et al., 1983 - U.S.A. study, and Bernard et al., 1976 - Belgian study.

Table 4.

Estimation of critical renal cortex concentrations of cadmium in workers

Renal cortex Cd µg/g	Reference and Method
174	Baader, 1952. Autopsy.
152-446	Axelsson and Piscator, 1971. Biopsy.
100-300	WHO Task Group, 1977. Autopsies and biopsies.
200-250	Roels et al., 1979. *In vivo* activation.
200-250	WHO 1980 (Roels et al., 1979)
300-400	Ellis et al., 1981. *In vivo* activation.
160-285	Roels, H.A. et al., 1981
216	Roels, H.A. et al., 1983

Table 5

Prevalence of proteinuria in cadmium workers

Cadmium compounds	Estimated concentrations in the air in $\mu g/m^3$	Exposure range in years	Number of examinees	Prevalence of proteinuria (%)	Method of detecting proteinuria	References
Cadmium oxide fumes	40-50	control	60	2	sulfosalicyclic acid method and tungstate method	King, E. Brit. J. Industr. Med. 12: 198-205 (1955. Bonnel, J.A. Brit. J. Industr. Med. 12: 181-195 (1955). Bonnel, J.A. et al. Brit. J. Industr. Med. 16: 135-147 (1959).
		1-9	37	24		
		>9	63	46		
	64-241[a]	control	11	0	tungstate method >100 mg/l	Tauchiya, K. Arch. Environ. Hlth. 14: 875-880 (1967).
		<1	4	0		
	123 (time-weighted average)	1-4	4	50		
		5-12	4	100		
Cadmium oxide dust	400-15,000	1-4	15	0	nitric acid method("Hellers test", positive in more than half the tests)	Friberg, L. Acta med. Scand. 138: Suppl., p. 240 (1950).
		9-15	12	33		
		16-22	17	41		
		23-34	14	64		
	130-1170	1-12	26	27	not stated	Horstowa, H. et al. Medycyna Prady, 17: 13-25 (1966)
	500	5-44	116	28	sulfosalicylic acid method	Adams, R.G. et al. Quart. J. Med. 38: 425-442 (1960).
	300-5000	5-44	13	15		
	50-1000	5-44	43	51		
	100-1000	5-44	40	20		
	50-200	5-44	20	0		

Cadmium compounds	Estimated concentrations in the air in µg/m³	Exposure range in years	Number of examinees	Prevalence of proteinuria (%)	Method of detecting proteinuria	References
	31[a](1.4)[b]	control	31	0	abnormal electrophoretic pattern as defined by the authors	Lauwerys, R. et al. Arch. Environ. Hlth. 28: 145-148 (1974).
		1-12(4)[c]	31	0		
	134 (88)[b]	control	27	4		
		0.6-19.7(9)[c]	27	15		
	66(21)[b]	control	22	0		
		21-40(28)[c]	22	68		
	0	control	87	3.4	radioimmuno-assay	Kjellstrom, T. et al. Environ. Res, 13: 303-317 (1977).
	50	0-3	50	6.0		
	50	3-6	30	6.6		
	50	6-12	21	19.0		
Cadmium stearate dust	30-690	control	24	17	qualitative trichloroacetic acid method	Suzuki, S. et al. Inuustr. Hlth, 3: 73-85 (1965).
		3	19	58		
Cadmium sulfide dust	114[d]	<1-5	12	17	electrophoresis	Harada, A. & Shibutanni, E. Kankyo Hoken Report No. 24, Tokyo, Japan Public Health Association, 1973, pp. 16-22 (in Japanese).
		5-21	7	100		
		<1-5	12	8	quantitative trichloroacetic acid method	
		5-21	7	43		

[a] Measured in the breathing zone.
[b] Respirable fraction (particle size <5 µm in diameter).
[c] The numbers in parenthesis are averages.
[d] Calculated average exposure for the worker with the most pronounced effect.

From Report of a WHO Study Group Technical Report Series 647. WHO Geneva. 1980.

Table 6.

Deposition of Unit Density Spheres

Tidal volume	Location	Diameter of sphere ())									
		0.01	0.06	0.20	0.60	1.0	2.0	3.0	4.0	6.0	10.0
750 cm^3	N-P	0	0	0	0	0.036	0.406	0.552	0.654	0.799	0.992
	T-B	0.307	0.068	0.027	0.020	0.027	0.051	0.071	0.084	0.091	0.007
	P	0.506	0.585	0.281	0.204	0.250	0.346	0.308	0.238	0.103	0.002
1450 cm^3	N-P	0	0	0	0	0.275	0.522	0.665	0.773	0.923	1.00
	T-B	0.256	0.051	0.017	0.019	0.027	0.050	0.064	0.069	0.043	0
	P	0.676	0.711	0.334	0.215	0.242	0.330	0.250	0.150	0.033	0
2150 cm^3	N-P	0	0	0	0.068	0.371	0.607	0.736	0.844	1.0	1.0
	T-B	0.208	0.035	0.015	0.021	0.030	0.056	0.067	0.062	0.0	0
	P	0.746	0.653	0.294	0.209	0.226	0.285	0.195	0.092	0.0	0

Taken from Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract, Health Physics, Vol.12 (1966).

Table 7.

Calculated Maximum Concentrations of Cadmium in the Kidney Cortex for Persons Not Occuaptionally Exposed to Cadmium Using Single Exponential Function

Biological Half-Life (years)	Smoker	Non-Smoker
10	28	20
21.5	55	40
33	73	54

Table 8a.

Calculated Maximum Concentration of Cadmium in Kidney Cortex µg/g for Persons Exposed for 30 or 45 Years to Cadmium in the Workplace, Using a Class Y Lung Model and a Single Exponential Function

Aerodynamic Diameter (microns)	Biological Half-Life / Cadmium Concn / Years Exposed	10 years						21.5 years						33 years					
		1 µg/m³		20 µg/m³		50 µg/m³		1 µg/m³		20 µg/m³		50 µg/m³		1 µg/m³		20 µg/m³		50 µg/m³	
		30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45
0.01		33	35	148	163	330	366	59	64	227	281	498	624	80	84	267	346	580	763
0.06		34	35	151	166	336	374	59	64	231	286	507	637	80	85	272	352	591	780
0.2		30	31	86	94	175	193	57	59	135	164	267	332	76	79	161	204	314	408
0.6		30	30	70	76	135	148	56	58	111	133	207	255	76	77	134	166	244	314
1		30	31	82	89	164	181	57	58	129	156	251	311	76	78	154	194	295	383
2		32	33	124	136	269	297	58	62	192	235	409	510	78	82	225	290	475	624
3		32	33	126	137	273	301	58	62	195	238	416	517	78	82	228	294	483	634
4		32	33	118	128	254	278	58	61	183	223	389	480	78	81	215	276	451	590
6		31	32	99	106	207	224	57	59	156	187	319	390	77	80	183	232	373	481
10		30	31	85	90	171	183	56	58	135	160	267	321	76	78	159	199	313	398

Table 8b.

Calculated Maximum Concentration of Cadmium in Kidney Cortex µg/g for Persons Exposed for 30 or 45 years to Cadmium in the Workplace, Using a Class W Lung Clearance Model and a Single Exponential Function

Aerodynamic Diameter (microns)	Biological Half-Life Cadmium Concns Years Exposed	10 Years						21.5 Years						33 Years					
		1 µg/m³		20 µg/m³		50 µg/m³		1 µg/m³		20 µg/m³		50 µg/m³		1 µg/m³		20 µg/m³		50 µg/m³	
		30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45
0.01		41	42	295	318	697	754	67	77	458	556	1076	1311	86	98	535	686	1253	1615
0.06		36	37	193	208	441	477	60	68	301	363	683	830	81	87	353	450	796	1024
0.20		31	32	104	111	219	236	57	59	165	196	341	412	77	80	194	244	399	510
0.6		30	31	83	89	167	179	56	58	133	157	261	315	76	78	157	196	306	390
1		31	32	102	109	214	231	57	59	162	193	334	403	77	80	190	240	390	499
2		35	37	187	201	426	461	60	67	292	352	660	802	81	87	342	436	770	990
3		37	38	209	225	481	520	61	69	325	393	744	905	82	89	381	486	867	1115
4		37	38	214	230	493	533	61	70	333	402	763	928	82	89	390	498	889	1144
6		36	38	207	223	476	515	61	69	323	390	737	897	82	88	378	482	859	1105
10		35	36	169	181	381	412	59	65	264	318	591	717	80	85	310	394	689	885

Table 8c.

Calculated Maximum Concentration of Cadmium in Kidney Cortex µg/g for Persons Exposed for 30 or 45 Years to Cadmium in the Workplace, Using a Class D Lung Clearance Model and a Single Exponential Function

Aerodynamic	Biological Half-Life	10 Years						21.5 Years						33 Years					
Diameter	Cadmium Concn	1 µg/m^3		20 µg/m^3		50 µg/m^3		1 µg/m^3		20 µg/m^3		50 µg/m^3		1 µg/m^3		20 µg/m^3		50 µg/m^3	
(microns)	Years Exposed	30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45
0.01		65	69	781	846	1911	2072	105	123	1206	1470	2944	3596	124	154	1404	1811	3425	4426
0.06		58	61	637	690	1552	1683	94	109	985	1200	2392	2921	112	137	1147	1478	2783	3595
0.20		42	44	315	340	747	809	69	79	489	594	1153	1406	87	100	572	733	1343	1732
0.6		38	39	237	255	551	596	63	72	369	446	852	1037	83	91	431	551	993	1278
1		41	43	304	328	720	779	68	78	473	573	1111	1354	86	99	552	707	1294	1668
2		56	59	602	651	1463	1586	91	106	930	1133	2255	2753	108	133	1084	1396	2624	3389
3		59	62	650	712	1603	1738	95	111	1016	1238	2470	3016	113	140	1184	1525	2873	3713
4		59	62	655	709	1596	1731	95	111	1012	1233	2460	3004	113	139	1179	1519	2862	3698
6		56	59	608	658	1478	1602	91	107	939	1144	2278	2782	109	134	1094	1410	2651	3424
10		53	55	533	577	1293	1401	86	100	825	1004	1993	2432	102	125	962	1238	2319	2995

Table 9.

Maximum Concentration of Cadmium in Kidney Cortex Calculated Using Eight Compartment Model

Cadmium Concentration in Air ($\mu g/m^3$)	Maximum Kidney Cortex Concentration			
	30 years Exposure		45 Years Exposure	
	Non-Smokers	Smokers	Non-Smokers	Smokers
0	32	43	32	43
1	42	49	42	49
20	141	148	158	164
50	298	305	342	348

TABLE 10

Authors (Year)	Study Population	Type of Design	No. Subjects (Deaths)	Duration of Follow-up	Avail. of Hygiene Data
Potts (1965)	British alkaline battery workers (current & former employees)	clinical study	unstated		
Kipling & Waterhouse (1967)	workers exposed to CdO 1 year (same plant)	letter (historical prospective)	246 not stated		
Sorahan (1982)	Ni-Cd battery workers (same plant)	historical prospective	3026 (591) & subcohort	June 30, 1980 (1940-1979)	CdO dust - some available
Sorahan (1983)	same plant	SMR & RMLT	3025 (693)	Jan. 31, 1981	
Holden (1980)	British Cd factory (Cd-Cu alloys)	historical prospective	347 CuCd dept. (158) 624 "vicinity" (263) 537 control (95) (brass & iron workers)	To Dec. 12/79 (started 1940-1962)	some available
Kjellstrom et al (1979)	Swedish Cd-Ni battery factory & (Cu-Cd alloy smelter)	historical prospective	269	1940 or after to 1974	some available CdO dust (CdO fumes)
Andersson et al (1982)	enlargement (only 1 plant alkaline battery factory)		528, exp. 1 year (118)	1940-1980	"
McMichael et al (1976a)	Active and retired rubber workers 4 cohorts - 4 plants	historical prospective	18,903 aged 40-84 (5160)	Jan. 1, 1964 x 10 years	multiple exposures
(1976b)	one of 4 plants	historical prospective	6,678 male rubber workers	same	same

Table 10 (Cont'd.)

Authors (Year)	Study Population	Type of Design	No. Subjects (Deaths)	Duration of Follow-up	Avail. of Hygiene Data
Lemen et al (1976)	Colorado cadmium smelter	historical prosp.	292 white males (92) - 89 with death certs.	2 year exp. Jan. 1, 1940 - Dec.31, 1969 followed to Jan. 1, 1974	some available
Thun et al (1984, unpubl.)	enlargement - same plant	historical prosp.	612 workers	followed to end of 1978	same
Armstrong & Kazantzis (1983)	English cadmium workers excluding Sorahan & Holden cohorts	historical prosp.	6,995 (1940) born after 1940	exposed 1 yr. 1942 - 1970 followed to end of 1979	relative (high, medium, low)
Inskip & Beral (1982)	Village of Shipham (Cd-exposed) and Hutton (non-exp.)	historical prosp.	501 Shipham (278) 410 Hutton (215)	identified in 1939 followed to Dec. 31, 1979	soil, diet

TABLE 11

CAUSE - SPECIFIC MORTALITY IN RELATION TO CADMIUM EXPOSURE

	EVER HIGH		EVER MEDIUM	
Cause of Death	O/E	SMR (95% CI)	O/E	SMR (95% CI)
All causes	41/41.0	100(69-131)	225/236.8	95(83-107)
All neoplasms	13/10.4	125(66-213)	55/59.7	92(68-116)
Lung cancer	5/4.4	113(37-263)	27/24.2	112(74-163)
Prostatic cancer	0/0.4	0(0-962)	0/2.5	0(0-147)

	ALWAYS LOW		TOTAL	
	O/E	SMR (95% CI)	O/E	SMR (95% CI)
All causes	1636/1689.0	97(92-102)	1902/1967.7	97(92-101)
All neoplasms	429/408.1	105(95-115)	497/478.2	104(95-113)
Lung cancer	167/157.0	106(90-123)	199/185.6	107(92-122)
Prostatic cancer	23/20.4	113(72-170)	23/23.3	99(63-148)

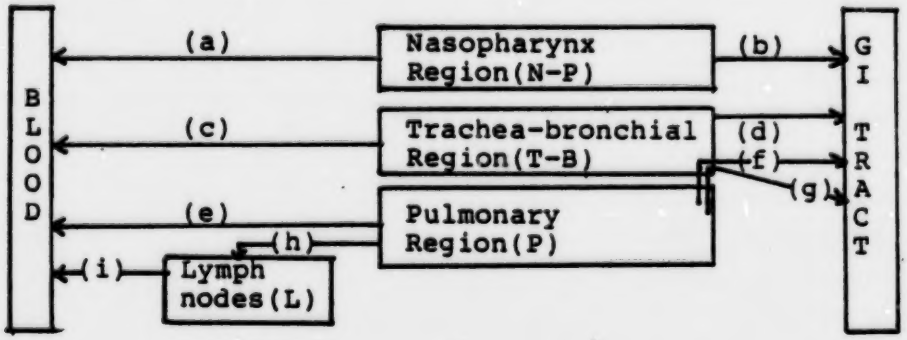
O = observed deaths. E = expected deaths. CI = confidence interval.

From Armstrong & Kazantzis (1983).

Figure 1

Amended Constants for Use with TGLM Clearance Model*

Region	Pathway	Compound Class (D)	(W)	(Y)
N-P	(a)	0.01 d/0.5	0.01 d/0.1	0.01 d/0.01
	(b)	0.01 d/0.5	0.4 d/0.9	0.4 d/0.99
T-B	(c)	0.01 d/0.95	0.01 d/0.5	0.2 d/0.01
	(d)	0.2 d/0.5	0.2 d/0.5	0.2 d/0.99
P	(e)	0.5 d/0.8	50 d/0.15	500 d/0.05
	(f)	-	1 d/0.4	1 d/0.4
	(g)	-	50 d/0.4	500 d/0.4
	(h)	0.5 d/0.2	50 d/0.05	500 d/0.15
L	(i)	0.5 d/1.0	50 d/1.0	1000 d/0.9

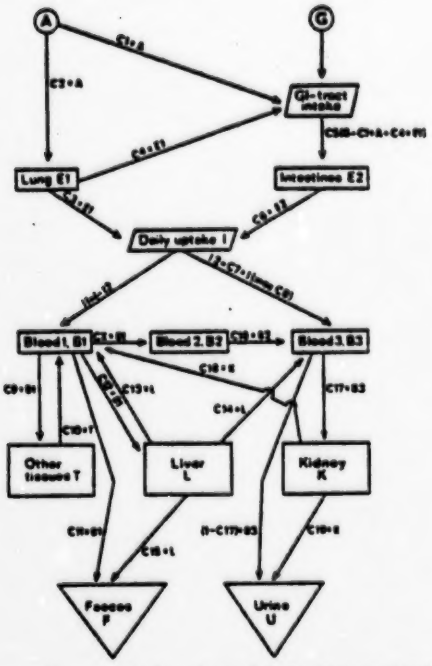


*The first value listed is the biological half-life; the second is the regional fraction.

Taken from Alkaline Earth Metabolism in Adult Man, Pergamon Press (1973).

Figure 2

MODEL OF CADMIUM METABOLISM



Flow scheme of the kinetic model of cadmium metabolism.

Taken from Kjellstrom, 1978.

Figure 3

Assumed and Modeled Values of Coefficients

Coefficient	Initially assumed ranges and unit [a]		Values fitting to empirical data
C1	0.1 - 0.2 (cigarette smoke) 0.4 - 0.9 (factory dust)		0.1 0.7
C2	0.4 - 0.6 (cigarette smoke) 0.1 - 0.3 (factory dust)		0.4 0.13
C3	0.01 - 0.3	day^{-1}	0.05
C4	0.1 x C3 = 0.001 - 0.03	day^{-1}	0.005
C5	0.03 - 0.1		0.048
C6	0.05	day^{-1}	0.05
C7	0.2 - 0.4		0.25
C8	0.5 - 5	Microgram	1
C9	0.4 - 0.8		0.44
C10	0.00004 - 0.0002	day^{-1}	0.00014
C11	0.05 - 0.5		0.27
C12	0.1 - 0.4		0.25
C13	0 - 0.0001	day^{-1}	0.00003
C14	0.0001 - 0.0003	day^{-1}	0.00016
C15	0 - 0.0001	day^{-1}	0.00005
C16	0.004 - 0.015	day^{-1}	0.012
C17[b]	0.8 - 0.98		0.95
C18	0 - 0.0001	day^{-1}	0.00001
C19[c]	0.00005 - 0.0002	day^{-1}	0.00014
CX	0.01 - 0.05		0.04
C20	0.05 - 0.5		0.1
C21	0 - 0.000002	day^{-1}	0.0000011

[a] If no unit is given, it means that the coefficient is a dimensionless proportion.

[b] C17 decreases from age 30 to age 80 by 33%.

[c] C19 increases from age 30 with C21 each year.

Taken from Kjellstrom, 1978.

Figure 4

MATHEMATICAL EQUATIONS

The flow of cadmium between the compartments in the model can be described by a series of differential equations. The accumulation curves of cadmium in each compartment can be calculated with an iterative procedure (iteration steps = one time unit) without solving the equations (i.e., numerical solution).[2]

Lung, exogenous compartment:

$$E1(t+1) = E1(t) + C2 \times A(t) - E1(t) \times (C3 + C4).$$

Intestines, exogenous compartment:

$$E2(t+1) = E2(t) + C5 \times [G(t) + C1 \times A(t) + C4 \times E1(t)] - C6 \times E2(t).$$

Daily absorbed amount of cadmium:

$$I(t+1) = C3 \times E1(t) + C6 \times E2(t).$$
$$I2(t+1) = C7 \times I(t+1) \leq C8.$$
$$I1(t+1) = I(t+1) - I2(t+1).$$

Blood compartment 1:

$$B1(t+1) = I1[t+1) + C10 \times T(t) + C13 \times L(t) + C18 \times K(t).$$

Blood compartment 2:

$$B2(t+1) = B2(t) - C16 \times B2(t) + B1(t) \times (1 - C9 - C11 - C12).$$

Blood compartment 3:

$$B3(t+1) = I2(t+1) + C14 \times L(t) + C16 \times B2(t).$$

Whole blood:

$$B4(t+1) = B2(t+1) + C20 \times [B1(t+1) + B3(t+1)].$$

Liver:

$$L(t+1) = L(t) + C12 \times B1(t) - L(t) \times (C13 + C14 + C15).$$

Kidney:

$C19(t) = C19$, if $t \leq 30$ years; $C19(t) = C19 + C21 \times n$, if $t > 30$ years
$n = 1, 2, 3 \ldots$; n increased once each year,

$$K(t+1) = K(t) + C17(t) \times B3(t) - C18 \times K(t) - C19(t) \times K(t).$$

Other tissues, endogenous compartment:

$$T(t+1) = T(t) + C9 \times B1(t) - C10 \times T(t).$$

Whole body:

$$W(t+1) = B4(t+1) + L(t+1) + K(t+1) + T(t+1) + E1(t+1) + E2(t+1).$$

Feces excretion (excluding nonabsorbed cadmium from G.I. intake):

$$F(t+1) = C11 \times B1(t) + C15 \times L(t).$$

Urinary excretion:

$$U(t+1) = B3(t) \times (1 - C17(t)) + K(t) \times C19(t).$$

The initially assumed ranges for the coefficients C1 to C21 are listed in Table 1.

[2] Footnote: The equations were programmed in BASIC and calculations were done by computer. The program can be made available for a nominal cost by the authors.

Taken from Kjellstrom, 1978.